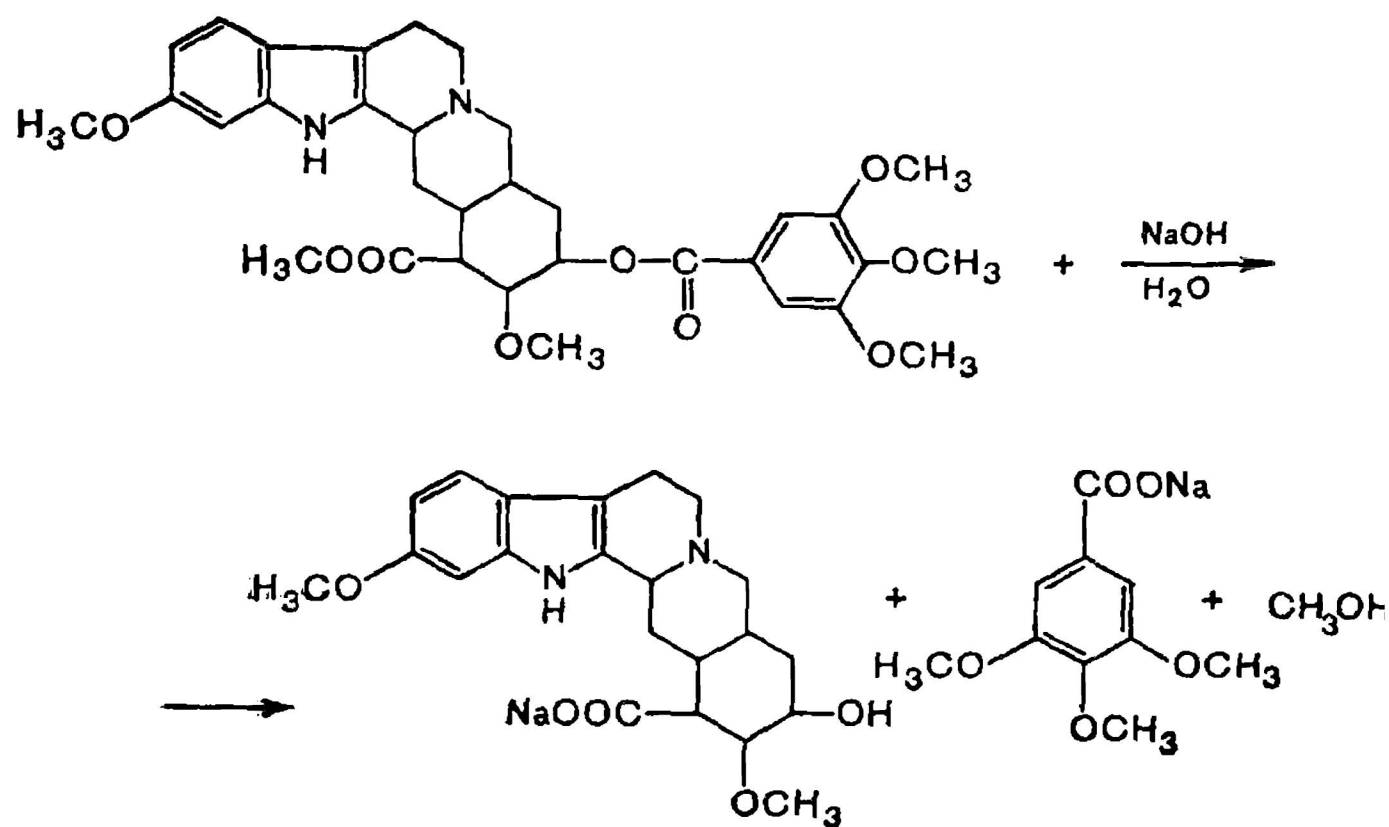


G.Melentyeva L.Antonova

Pharmaceutical Chemistry



Mir Publishers Moscow

G. Melentyeva

L. Antonova

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Г. А. Мелентьева
Л. А. Антонова

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G. Melentyeva

L. Antonova

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Preface

Having united our experience gained from instruction in higher and secondary schools, we have written a book for students of pharmaceutical schools that attempts to combine theory and laboratory applications. This has been done for the first time and substantially distinguishes the present textbook from those issued previously on the subject.

The latest achievements in pharmacology and related disciplines resulted in the appearance of a multitude of new drugs and medicinal preparations and the development of more improved methods for their analysis.

The first part of the book acquaints students with modern physicochemical methods of analysis, a general idea of which is needed for their future work. The other three parts are devoted to a description and the analysis of inorganic and organic drugs and selected groups of biologically active natural compounds (alkaloids, vitamins, antibiotics).

Each chapter ends with review questions intended to help students ascertain how thoroughly they have understood and mastered the material. The instructor can also use these questions for testing the students.

Most chapters are followed by laboratory experiments with a detailed description of procedures. The chemical substantiation of the reactions, the observations, and conclusions are the students' responsibility. The practical lessons help students gain laboratory skill. Moreover, they contain elements of the problem solving research method. The chapters "Aromatic Acids and Their Derivatives" (Chap. 20), "Phenol Acids and Their Derivatives" (Chap. 21), and "Glycides and Their Derivatives" (Chap. 29) use this method. Students should analyse the same substance by different methods and establish the advantages of one over another. But the recommended experiments are not proposed dogmatically; they can be replaced by the pharmacopoeial analysis of substances, or the analysis of one drug or medicinal form can be replaced by another depending on the laboratory facilities available. More often, experiments with identification reactions and quantitative analysis are suggested because they require quick thinking and vary in the procedure followed. Experi-

ments involving the determination of drug purity are proposed less frequently because in a pharmacy only identification reactions and quantitative analysis are performed.

Students are invited to analyse a number of substances in accordance with the pharmacopoeia and other official sources used in their country.

The appendices contain brief information on a number of frequently encountered drugs (including new ones), the analysis of several medicinal forms indicated in rather complex prescriptions often issued by physicians, and refractometric tables used in refractometric analysis.

We wish to express our gratitude to all our colleagues for their helpful suggestions.

Galina Melentyeva
Lidiya Antonova

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Introduction

PHARMACEUTICAL CHEMISTRY AND ITS RELATION TO OTHER SCIENCES

Pharmaceutical chemistry is a science that makes use of the general laws of chemistry to study drugs, i.e. their preparation, chemical nature, composition, structure, influence on an organism and studies the physical and chemical properties of drugs, the methods of quality control, and the conditions of their storage.

Pharmaceutical chemistry occupies the most important place among the related sciences (e.g. drug technology, toxicological chemistry, pharmacognosy, the economy and organization of the pharmacy).

At the same time, pharmaceutical chemistry, being a specialized science, depends on other chemical (inorganic, organic, analytical, physical, and colloid chemistry) and also on medico-biological (pharmacology, physiology, biological chemistry) disciplines.

A knowledge of the biological disciplines is needed to understand the complex physiological processes based on chemical and physical reactions that occur in an organism. This makes it possible to use drugs more rationally, observe their action on an organism, and control the molecular structure of the drugs being developed to obtain the desired pharmacological effect. The results of pharmacological tests of drugs determine the possibility of using them in medical practice.

The action of a drug is determined not only by its chemical structure, but also by its physicochemical properties. This is why pharmaceutical chemistry is closely related to physical and colloid chemistry. Without a knowledge of organic and analytical chemistry, it is impossible to study the molecular structure of a drug and to develop methods for its synthesis and analysis. Questions about the compatibility of drugs in a prescription, the production methods, the expiration dates, and the conditions for the storage and dispensing of drugs relate pharmaceutical chemistry to the technology of drugs and to the economics and organization of the pharmacy. But the problems concerned with the compatibility of drugs and the conditions for their storage can be solved only by a specialist well acquainted with pharmaceutical chemistry.

At its present stage, pharmaceutical chemistry is closely related to physics and mathematics. The physicochemical methods of analysis of drugs and calculations in pharmaceutical analysis are based on the general laws of these sciences.

A BRIEF HISTORICAL OUTLINE

The appearance of pharmaceutical chemistry as a science relates to the beginning of the 16th century, when alchemy* gave way to iatrochemistry (medical chemistry) whose founder was Theophrastus Paracelsus (1493-1541). "Chemistry must serve the protection of health instead of procuring gold," Paracelsus proclaimed.

The basis of Paracelsus' teachings was the explanation of vital processes from the viewpoint of chemical transformations. During this period, chemical preparations were widely used as drugs along with drugs of a plant origin.

Paracelsus was the first to introduce the concept of the active principle as a chemical substance. Compounds of various metals such as mercury, lead, copper, iron, antimony, and arsenic were employed for medical purposes. Pharmacies of that period were like scientific research laboratories where the healing effect of both chemical and plant-derived medicinal agents was tested. This was the origin of pharmaceutical analysis. The period of iatrochemistry can be considered as the period of the appearance of pharmaceutical chemistry.

The period of iatrochemistry in the second half of the 17th century gave way to a new trend in pharmaceutical chemistry, in which the leading place was occupied by the phlogiston theory (Gk *phlogistos* inflammable). J. Becher (1635-1682) and G. Stahl (1660-1734), supporters of this theory, attempted to explain the phenomena of combustion and oxidation as the decomposition of the body during which phlogiston (phlogiston in Stahl's opinion was the general "principle" which all bodies contain) separates and the other constituent part of the body remains. Hence, according to the phlogiston theory, only complex bodies could burn. This theory was refuted by the great Russian scientist M. Lomonosov (1711-1765), who proved that the leading role in the processes of combustion and oxidation is played by the oxygen of the air, and that combustion is not a decom-

* Alchemy was a prescientific trend in the development of chemistry. It first took shape in Egypt (3rd-4th centuries A.D.) and developed widely in Western Europe (9th-16th centuries). The main purpose of alchemy was to find the "philosophers' stone" used for transforming base metals into gold and silver, for preparing the elixir of longevity, etc. This period saw the discovery or improvement of ways of producing some valuable products (mineral and plant-derived paints, enamels, glass, metallic alloys, acids, alkalies, salts, drugs), and also the development of some laboratory techniques (distillation, sublimation, etc.).

position reaction with the evolution of phlogiston, but, conversely, a combination reaction during which the burning substance combines with the oxygen of the air.

The remarkable discoveries of this period are associated with the names of pharmacists. Thus, the Swedish pharmacist K. Scheele (1742-1786) produced tartaric acid from tartar and discovered the organic citric, malic, oxalic, lactic, gallic, and uric acids. He also discovered glycerin, chlorine, manganese, and hydrocyanic acid. Scheele was the first to produce oxygen.

The second half of the 18th century is characterized by substantial development and achievements in organic chemistry. The pharmacists of this period made a number of important discoveries that played a major role in the further development of pharmaceutical chemistry. For example, L. Vauquelin (1763-1829), the first head of the pharmaceutical school in Paris, discovered the elements chromium, beryllium, palladium, and osmium.

The pharmacist B. Cortois (1777-1838) isolated mineral salts from seaweed ashes and discovered iodine. The French pharmacist A. Seguin (1767-1835) was the first to derive morphine (crude) from opium (1807), while later the pharmacist F. Serturner (1783-1841) isolated morphine in the crystalline form, determined its basic properties and its ability to form salts with acids.

The French pharmacists P. Pelletier (1788-1842) and J. Caventou (1795-1877) separated quinine, strychnine, brucine, and other alkaloids from natural plant sources.

The German pharmacist K. Mohr (1806-1879) made significant contributions to the volumetric analysis of drugs. He was the first to use burettes and pipettes in analysis, and invented the balance bearing his name.

Thus, pharmacies played a major role in the birth and development of pharmaceutical chemistry.

In Russia, pharmacies appeared much later, but their role was the same. They performed the function of chemical laboratories where pharmacists worked side by side with alchemists, who were called pharmacy chemists and produced and analysed chemical preparations.



Theophrastus Paracelsus
(1493-1541)



M. Lomonosov (1711-1765)

The first Russian alchemist T. Ananyin was engaged in the production of pharmaceutical preparations, using both foreign books and Russian "herb books".

By the middle of the 18th century, chemistry in Russia had become quite developed. Its development is associated with the name of the outstanding scientist M. Lomonosov who made a large contribution to medicine, chemistry, and pharmacy and who is rightfully called the Russian scientist-encyclopedist. He initiated quantitative analysis in analytical chemistry, developed physical chemistry, indicated the significance of mathematics and physics in chemical research, discovered the law of mass conservation, advanced the

kinetic theory of heat, and so on. In his work "Slovo o pol'ze khimii" (Some Words on the Usefulness of Chemistry), Lomonosov pointed out the leading role of chemistry in the development of medicine and pharmacy. He founded the first scientific chemical laboratory in Russia (1748) in which he performed experiments and trained students in experimental chemistry.

T. Lowits and V. Severgin were worthy successors of Lomonosov. They continued his work and made many new discoveries.

Academician T. Lowits (1757-1804) discovered the adsorptivity of charcoal and proposed employing it for the purification of alcohol, and then of water. He was the first to obtain glacial acetic acid and to apply the microcrystalloscopic method of analysis in practice. Academician V. Severgin (1765-1826) devoted much time to developing procedures for the qualitative and quantitative analysis of drugs. He was the first to publish in Russian a book on pharmaceutical analysis entitled *A Way of Testing the Purity and Authenticity of Chemical Medicinal Preparations*. This was the first guide to pharmaceutical chemistry in Russia. He also published a number of other works that played a major role in the further development of pharmaceutical analysis.

An outstanding figure in Russian pharmacy was Professor A. Iovskiy (1796-1857) who contributed greatly to the development of chemical and pharmaceutical theory and practice. One of his numerous works, *Chemical Equations with a Description of Various Ways of Determining the Content of Chemical Substances* (in Russian), laid



T. Lowits (1757-1804)



V. Severgin (1765-1826)

the scientific foundation for the development of the quantitative analysis of pharmaceutical preparations.

An important contribution to scientific and practical pharmacy was made by the eminent Russian scientist and public figure A. Nelyubin (1785-1858). He obtained a large number of drugs, developed new and improved the existing methods of preparing them. His work *Pharmacography* (in Russian) in four volumes was the first Russian encyclopedic guide to medicinal drugs. It described all the medicinal preparations known at that time. One of his students, Yu. Trapp, wrote the book *Pharmaceutical Chemistry* (in Russian, 1885).

An important feature of modern pharmaceutical chemistry is the introduction of more refined and sensitive methods of physicochemical analysis such as photometry and chromatography that enable one to assay the quality of drugs more accurately and with the smallest consumption of the analyte, reagents, and time.

In recent years, a new trend has appeared, namely, biopharmaceutical analysis, i.e. the determination of drugs and their metabolites in the biological substrates of an organism.

The basic trends in pharmaceutical analysis at present are the further improvement of physicochemical methods of analysis of pharmaceutical preparations and their widespread practical application in the relevant establishments (pharmacies, analytical and control laboratories), the development of simple methods for analysing complex medicinal mixtures in pharmacies, the development and improvement of the analysis of new drugs, especially of the group of complex natural substances with strong biological action (cardiac glycosides, hormones, vitamins, antibiotics), studying the

conditions of storage of chemico-pharmaceutical preparations, drugs, and galenicals in various climatic zones, studying the effect of high-polymer compounds (packing material) on the action of drugs, and the further development and improvement of biopharmaceutical analysis.

RAW MATERIALS FOR DRUGS

All drugs in their nature are divided into inorganic or organic. Both can be prepared from natural sources or artificially, i.e. synthetically. Various minerals and ores, gases, the water of lakes and seas, etc. are the raw materials used in the production of inorganic drugs. Some of them are produced from the residues of other production processes.

The raw material base of the USSR is sufficient to completely meet the demands of the chemico-pharmaceutical industry.

Organic drugs are chiefly produced from petroleum, natural gas, coal, and wood.

Petroleum can be processed to yield substances employed in medicine such as petroleum jelly (vaseline), liquid paraffin (vaseline oil), paraffin, aromatic hydrocarbons, and their derivatives.

In the dry distillation of coal, one of the fractions is coal tar, which is a source for the production of mainly phenols and their derivatives. Phenol, which is an antiseptic itself, can be processed to yield benzene, toluene, and naphthalene. These are the initial substances for the synthesis of many drugs.

Methanol, acetic acid, etc. are produced from the pyroligneous liquor obtained in the dry distillation of wood.

Combustible shale, which is rich in sulphur, is a valuable natural medicinal raw material. The products of the dry distillation of shale go to produce ichthammol, and also many drugs that are derivatives of the heterocyclic series.

Raw material of a plant and animal origin is a very valuable source for the production of many drugs.

Raw material of an animal origin includes the organs of healthy animals (tissues, glands). For example, thyroïdin is produced from the thyroid gland, adrenaline (epinephrine), from the adrenal medulla of the adrenal glands, cortisone, from the adrenal cortex of the adrenal glands, and so on.

Numerous and diverse species of plants are a very rich source for the production of important drugs, alkaloids, glycosides, vitamins, essential oils, resins, chyle, and fatty oils. In part, these products are themselves used in pharmaceutical preparations; for example, essential oils (peppermint, rose, lavender and other oils), while others, after the appropriate treatment, become medicaments.

The present variety of drugs is being supplemented with a new group of drugs having a strong biological action, namely, antibiotics, whose origin is chiefly microorganisms.

CLASSIFICATION OF DRUGS

The enormous number of diverse drugs used in medicine has made it necessary to classify them. The following classification systems are possible.

Pharmacological classification—drugs are divided depending on their action on an organism (the heart, brain, lymphatic system, stomach, intestines, etc). Accordingly, drugs are divided into such groups as narcotics, soporifics, analgesics, diuretics, and local anaesthetics.

Chemical classification—drugs are grouped according to their chemical structure and properties regardless of their pharmacological action.

Both classifications are not deprived of shortcomings: the pharmacological classification quite often groups drugs with a common physiological action, but of the most diverse structures. The group of cardiac stimulants includes representatives of the heterocyclic series, both natural (caffeine, strychnine) and synthetic [corazol (pentetrazole), cordiamin (nikethamide)], and a representative of terpenes (camphor) and cardiac glycosides, which are steroid compounds. The chemical classification has a similar shortcoming. Here substances similar in structure have absolutely different physiological actions. Moreover, the chemical structures of newly obtained substances, especially complex natural ones, may for some time be controversial and unclear, therefore their inclusion in a specific structural group can be quite relative, and sometimes erroneous. In this connection, a mixed classification system is sometimes used, where both features are taken into account. Modern science and engineering, however, are constantly improving the methods of establishing the structure of newly developed drugs. This is why greater and greater preference is being given to the chemical classification, whose main advantage is that it enables the relation between the chemical structure of a drug and its action on an organism to be ascertained.

Drugs are also classified with respect to their action on an organism into groups A, B, and C.

Group A includes poisonous drugs whose improper administration may result in a toxic effect.

Group B includes highly potent drugs whose doses must be carefully monitored to prevent overdosage.

Group C includes all other drugs.

PHARMACOPOEIA AND OTHER DOCUMENTS CONTROLLING DRUG QUALITY

Every country has legislation on pharmaceutical preparations that sets standards and obligatory quality indices for medicaments, raw materials, and preparations employed in the manufacture of drugs. These regulations are presented in separate articles—general and specific—relating to individual drugs, and are published in the form of a book called a pharmacopoeia.

The USSR State Pharmacopoeia is based on the principles of Soviet health protection and on the modern achievements in medicine and other branches of science. It indicates how drugs are to be analysed (assayed). The quality requirements for drugs set forth in the Pharmacopoeia are obligatory for all organizations and enterprises in the Soviet Union having to do with the manufacture, storage, control, and use of drugs.

The pharmacopoeia of every country is revised periodically to take account of the replacement of obsolete drugs by new ones and of changes in the methods of analysing drugs.

The first pharmacopoeia in Russian was published in 1886. The first Soviet Pharmacopoeia was published in 1925 (the 7th edition of the State Pharmacopoeia). At present, the 10th edition of the State Pharmacopoeia is in force (the 11th edition is being prepared for publication). In the 9th and 10th editions of the State Pharmacopoeia, the international chemical nomenclature is used in the Latin chemical terminology of drugs in accordance with the **International Pharmacopoeia** (*Pharmacopoeia Internationalis*). This was necessary for the development of international trade in drugs. The chemical names of organic drugs used in the USSR are also based on the principles of the international chemical nomenclature.

Constant collaboration between countries in the field of public health and drug production necessitated the establishment of common, unified requirements for the quality of drugs, and, consequently, unified methods of analysing them. For this purpose, the International Pharmacopoeia was created. It is published under the auspices of the World Health Organization and is a collection of recommended requirements on drug quality. The International Pharmacopoeia is not a legal document for any country, but it provides the basis for establishing national requirements on drug quality. At present, the 2nd edition of the International Pharmacopoeia (published in 1968) along with the supplement to it (1971) are in use. Specialists of many countries, including the USSR, took part in preparing the second edition of the International Pharmacopoeia. In 1981, the first volume of the 3rd edition of the International Pharmacopoeia was published. It contains general methods of analysis.

As a result of the constantly expanding collaboration between the socialist countries (members of the Council for Mutual Economic Aid) in the fields of public health and drug production, it became necessary to unify the standards for drug quality and the methods of analysing them. For this purpose, the *Compendium medicamentorum* was published in 1970 in both Russian and German.

In the present book, all references are to the 10th edition of the USSR State Pharmacopoeia. Students are invited to compare the relevant tests for individual drugs with those of the pharmacopoeia used in their country and should keep these differences in mind in their future work.

CAUSES OF POOR DRUG QUALITY. GENERAL REQUIREMENTS FOR DRUG PURITY

Pharmaceutical analysis deals not only with medicaments, but also with their precursors, i.e. with the raw material on whose degree of purity the quality of the drugs depends.

The quality of a drug is determined, after establishing its authenticity, by testing its purity and the quantity of the pure substance in the drug. The determination of all these indices forms the basis of pharmaceutical analysis, and the results for each drug must strictly correspond to the requirements of the State Pharmacopoeia. Generally, almost all drugs contain impurities. The contamination of drugs by various admixtures may not only lower their therapeutic effect, but also cause undesirable sideeffects. Admixtures that can poison an organism are especially dangerous.

The causes of the appearance of admixtures in drugs can vary, and this is a natural occurrence. Contamination can be due to poor purification of the initial raw material, and to the presence of by-products of synthesis, mechanical impurities (remnants of filtering materials such as fabric, filter paper, and asbestos), and residues of solvents (alcohol, water, etc.). The material of the apparatus used for the production of a drug can also contaminate a drug. Metallic apparatuses can be a source of lead (from utensils), iron, copper, sometimes zinc, and (the most dangerous) arsenic contamination. Admixtures can also appear in drugs when their storage conditions are violated. For example, when chloroform for narcosis is stored improperly (in the light with the access of air), it becomes oxidized; the oxidation products—phosgene and hydrochloric acid—not only diminish its narcotic action, but can also result in phosgene poisoning of the patient.

Some drugs require storage conditions that exclude the slightest infiltration of moisture because it can cause hydrolytic decomposition of the drug or the growth of microorganisms. For example, drugs having the structure of esters (acetylsalicylic acid, atropine sulphate,

etc.) can hydrolyze in the presence of moisture. This not only lowers the effect of the drug, but may also poison the organism with toxic hydrolysis products. But there are also drugs that must contain water to exhibit the required action, e.g. magnesium sulphate MgSO_4 (a purgative).

It is very important to observe the specific storage conditions for drugs containing water of crystallization, especially for those containing poisonous substances (arsenic, mercury, etc.). Thus, if the crystallization water evaporates from the arsenic drug sodium arsenate, $\text{Na}_2\text{HAsO}_4 \cdot 7\text{H}_2\text{O}$, while the dose is given with account of seven water molecules, with the same dose the patient will receive a larger amount of arsenic than is needed and may even be poisoned.

Many impurities in drugs are non-volatile with a large content of inorganic substances (the ash residue). In the majority of cases, the ash does not contain harmful admixtures such as heavy metals and arsenic (for which tests are recommended when analysing a drug), and therefore the State Pharmacopoeia tolerates a definite limit of the ash content for each drug.

When establishing the quality of a drug, account must also be taken of the physiological action of the admixtures. Sometimes a specific amount of an admixture is tolerated in one drug, but is strictly prohibited in another. For example, if sodium chloride used for the preparation of an isotonic solution contains an admixture of potassium salts, it cannot be used in medicine because physiologically the potassium ions are antagonists to the sodium ions. Therefore, an admixture of potassium salts in sodium chloride is strictly prohibited. On the other hand, the same admixture in another preparation, for example, in calcium chloride, is not dangerous, and hence the State Pharmacopoeia allows it in a limited amount.

The State Pharmacopoeia limits an admixture of magnesium salts in calcium salts and vice versa because these two elements are also antagonists.

Thus, in tests for purity, depending on the nature of the substance being tested and the harm potentially caused by a specific admixture, the State Pharmacopoeia either requires the complete absence of admixtures, or indicates a maximum permissible limit of the admixtures in a given drug that will not influence its quality or healing effect.

To determine the tolerated limit of admixtures in a drug, the State Pharmacopoeia has introduced what are called **reference or standard solutions**.

The results of a test reaction for a definite impurity in a drug are compared with those of a reaction conducted with the same reagents and in the same volume but with a standard solution containing the tolerated amount of the admixture. A comparison of the solutions being studied (analyte solutions) with the standard one makes it

possible to determine the absence or presence of the admixture and whether it is contained in a larger or smaller amount than that in the standard prepared in accordance with the requirements of the State Pharmacopoeia.

When analysing (assaying) drugs, one must take the exact quantities of the reagents that are recommended by the pharmacopoeia, otherwise the sought admixture may fail to be detected. Pharmacopoeial analysis often indicates the time during which a reaction must be observed. Only when all the requirements specified in the pharmacopoeia to the analysis of drugs are observed can one be certain that it has been performed properly.

I. Methods of Investigating Drugs

The methods of investigating medicinal agents are divided into physical, chemical, physicochemical, and biological ones.

Physicochemical and physical methods are used the most.

Physical methods of analysis involve the studying of the physical properties of a substance. They include determination of the solubility, transparency or degree of turbidity, colour, density or specific gravity (for liquids), moisture content, and melting, freezing, and boiling points. The relevant procedures are described in the State Pharmacopoeia.

Chemical methods of investigation are based on chemical reactions. They include the determination of the ash content, the hydrogen ion concentration (pH) of a medium, and characteristic numerical indices of oils and fats (the acid number, iodine number, saponification number, etc.).

Only such reactions are used to identify drugs that are attended by a noticeable external effect, for example, by a change in the colour of a solution, the evolution of gases, and the formation or dissolution of precipitates.

The chemical methods also include the gravimetric and volumetric methods of quantitative analysis employed in analytical chemistry (the method of neutralization, precipitation, redox methods, and so on). Recently, titration in non-aqueous media and complexometry have been introduced into pharmaceutical analysis.

Qualitative and quantitative analyses of organic drugs are generally carried out with respect to the functional groups in their molecules.

Physicochemical methods are used to study the physical phenomena that occur as a result of chemical reactions. For example, in the colorimetric method, the colour intensity is measured depending on the concentration of a substance, and in conductometric analysis the electrical conductivity of solutions is measured as a function of their concentration.

Among the physicochemical methods are optical (refractometry, polarimetry, emission and fluorescence methods of analysis, photometry including photolorimetry and spectrophotometry, nephelo-

metry or turbidimetry), electrochemical (potentiometry, polarography), and chromatographic methods.

Recently, various kinds of chromatography (column, paper, thin-layer, gas, gas-liquid) and of photometric methods based on the absorption of light by the analytes have found their way into pharmaceutical analysis. Methods involving nuclear reactions such as nuclear magnetic resonance (NMR) and paramagnetic resonance (PMR) are becoming more and more popular.

Non-aqueous solvents are widely used in modern pharmaceutical analysis. Previously the main solvent in analysis was water, while at present a variety of non-aqueous solvents (glacial or anhydrous acetic acid, acetic anhydride, dimethylformamide, dioxan, etc.) are also used. They allow the basicity and acidity of the analytes to be varied. A micromethod, in particular the drop method of analysis, has been developed. It is convenient for use in pharmacies for controlling the quality of drugs.

Combinations of various methods are being employed in the analysis of drugs. For example, the combination of mass spectrometry with gas chromatography is one of the most powerful analytical tools available. Physics, quantum chemistry, and mathematics are employed more and more in modern pharmaceutical analysis.

The analysis of any drug or raw material must be begun with an examination of the colour, odour, form of the crystals, container, packing, and colour of the glass. This is followed by the taking of an average sample in accordance with the official requirements.

Chapter I. Chemical Methods*

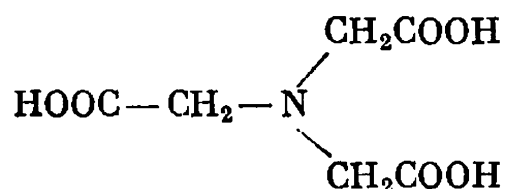
1.1. THE COMPLEXOMETRIC METHOD OF TITRATION

Among the volumetric methods of analysis adopted by the State Pharmacopoeia for the quantitative determination of drugs, the **complexometric** method of titration (also known as complexation titration or complex-formation titration) has been widely introduced. It is based on the reaction of formation of stable complexes of polyaminocarboxylic acids with metal ions (Ca^{2+} , Mg^{2+} , Zn^{2+} , Bi^{3+} , etc.). These acids are called **complexing agents** (sometimes the term com-

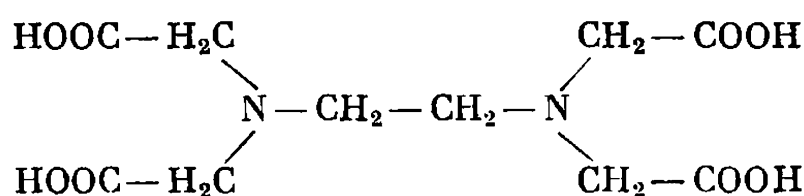
* In this chapter, we have omitted a description of the volumetric methods of quantitative analysis, which are well known to students from the course in analytical chemistry (the methods of neutralization, precipitation, and oxidation-reduction), but treat the methods of complexometry and non-aqueous titration, which are widely used at present in pharmaceutical analysis.

plexone is used to denote them). The following are the simplest complexing agents*:

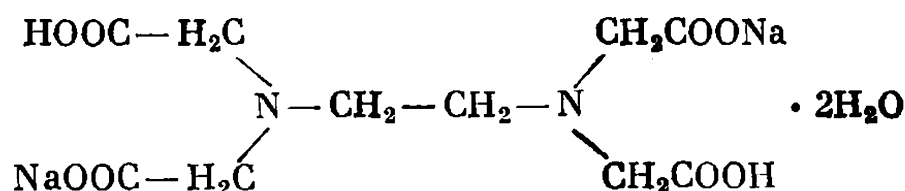
tribasic nitrilotriacetic acid (NTA or complexon I) or H_3Y , where Y^{3-} is the anion:



ethylenediaminetetraacetic acid—EDTA (also known as ethylenedinitrilotetraacetic acid) (complexon II):

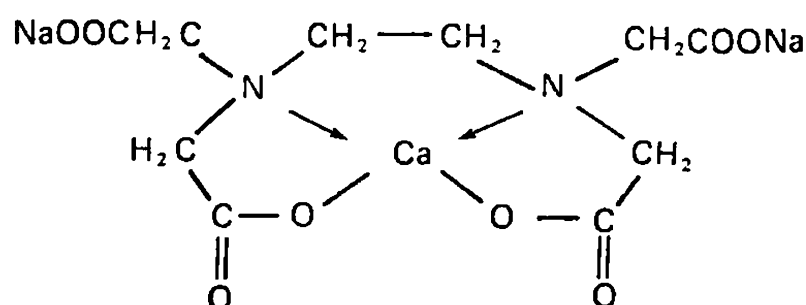


the disodium salt of ethylenediaminetetraacetic acid $\text{Na}_2\text{H}_2\text{Y}$ or Na-EDTA (complexon III):



* Complexing agents are widely used in analytical chemistry, as well as in engineering and medicine. The ability of complexing agents to form complexes with metal ions is employed to discharge toxic metal ions including radioactive ones from an organism. The most widely used are ethylenediaminetetraacetic acid (EDTA) and its sodium salt (Na-EDTA). The acid is often used to eliminate the hardness of water, because it binds Ca^{2+} into a soluble complex. Na-EDTA is used in medicine to eliminate calcium ions when this element is deposited in a body under pathological conditions. It is also used to prevent the coagulation of blood being preserved, which is also based on the binding of the calcium ions.

The calcium salt of Na-EDTA (the disodium-calcium salt of EDTA) known as tetacin-calcium (sodium-calcium edetate) is also used in medicine. A 10% solution of this salt is a pharmacopoeial preparation:

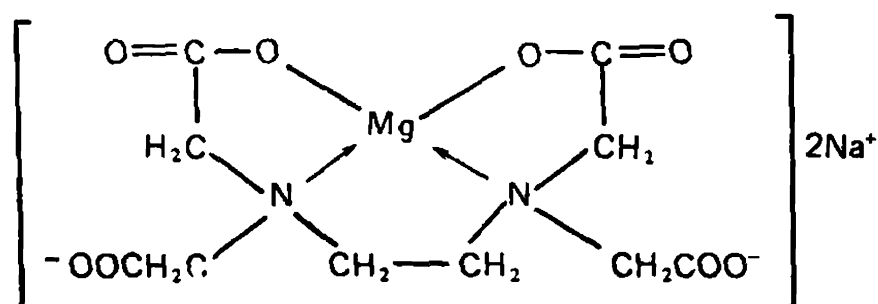


It is used as an antidote in poisoning with salts of the heavy metals. Its effect is based on the fact that the calcium in the molecule can be replaced by ions of the heavy metals, including toxic ones, to form complexes with a low toxicity soluble in water. These complexes are rapidly secreted from the body via the kidneys.

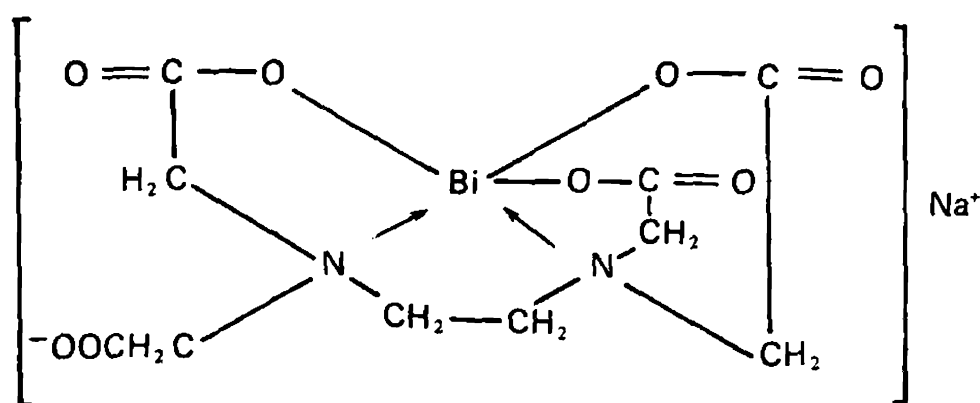
All these complexing agents can be used as titrants in the quantitative analysis of heavy metal salts. Na-EDTA is used most for this purpose.

Na-EDTA contains amine nitrogen in addition to carboxyl groups and is therefore an acid and complexing agent. Many metals are capable of replacing the hydrogen atoms of the carboxyl groups in Na-EDTA. The metals are bound to the amino group nitrogen by a coordination bond and stable complexes of the Na-EDTA with the relevant metal are formed.

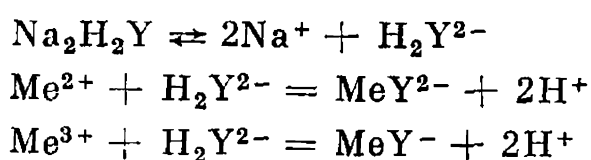
A doubly charged cation (for example, Mg^{2+}), forms a complex with Na-EDTA having the following composition:



The structure of the complex formed by a triply charged cation (for example, Bi^{3+}) with Na-EDTA is as follows:



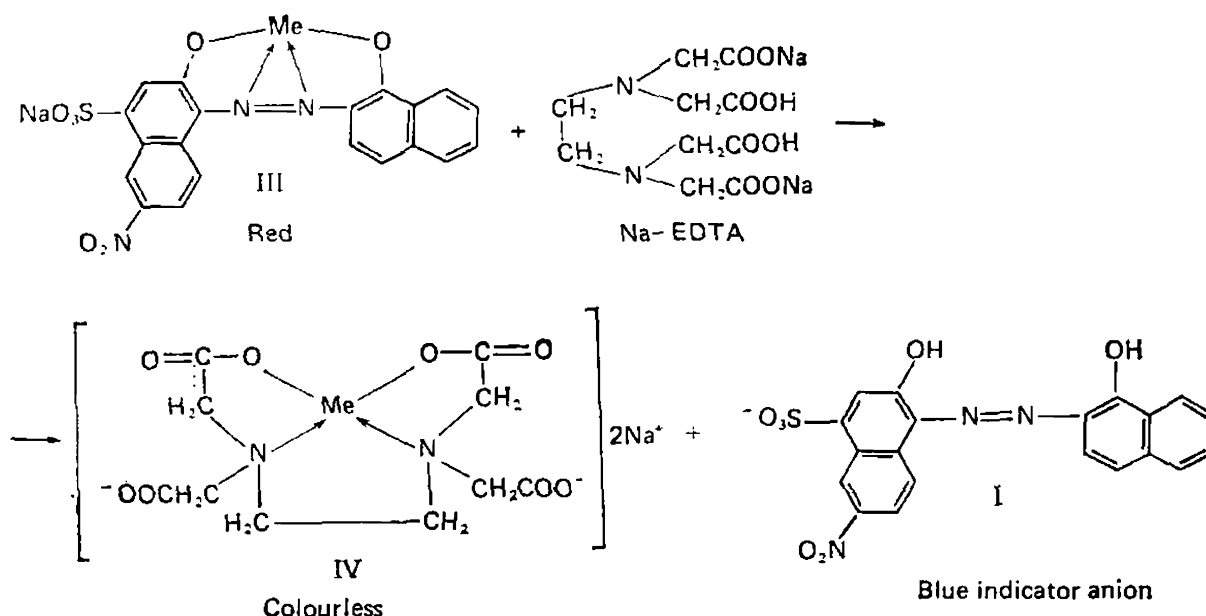
The formation of the above complexes can be represented schematically as follows:



where $\text{Na}_2\text{H}_2\text{Y}$ is Na-EDTA, and Me^{n+} is a metal ion.

A glance at the above scheme reveals that a reaction of complex formation is attended by the accumulation of an acid in the solution, therefore the binding of the H^+ ions should facilitate the formation of a complex.

EDTA into a more stable complex (IV). The indicator anion (I) passes into the solution and colours it blue:



The solution's colour changes distinctly in an alkaline medium (pH = 8-10).

The principle of complexometric titration thus consists in the following. A small amount of the relevant indicator is added to the analyte solution containing the cation being determined at a strictly definite pH. A coloured complex of the indicator with the cation forms that is well soluble in water. In titration with Na-EDTA, this complex decomposes, and a more stable, generally colourless, complex of the cation with Na-EDTA forms. The indicator anion is liberated and imparts a different colour to the solution. This colour is characteristic of the free indicator at the given pH.

Complexometric titration is performed in two ways, namely, by titration and back-titration. Most cations are determined in an alkaline medium by titration.

Back-titration is employed when the analyte cations are being precipitated with ammonia (a component of an ammonia buffer solution), or when the ions of a metal, for example aluminium, react very slowly with Na-EDTA. In this case, a definite excess of Na-EDTA is added to the analyte salt solution, and is titrated with a solution of a salt, most frequently of Zn²⁺ or Mg²⁺, using a definite indicator and a definite value of the pH.

At the equivalence point, the colour of the solution changes from that of the free indicator to that of its complex with the metal cation of the salt whose solution was used to titrate the excess of Na-EDTA.

The following conditions must be observed in complexometric titration:

at the equivalence point the metal cation should be practically completely bound into a complex with Na-EDTA;

the complex of Na-EDTA with the cation being determined must be more stable than that of the indicator with this cation.

The complexometric method is recommended by the State Pharmacopoeia for determining the content of a substance in preparations that are salts of metals such as calcium, magnesium, zinc, copper, and mercury.

1.2. ACID-BASE TITRATION IN NON-AQUEOUS MEDIA

Titration in non-aqueous media has definite advantages in comparison with titration in aqueous media and is constantly gaining popularity. The main advantage of this method is that not only strong acids and bases, but also weak and very weak acids, bases, and their salts can be titrated with sufficient precision, while multi-component mixtures can be titrated without their preliminary separation. This method makes it possible to determine the physiologically active part in salts of alkaloids. Moreover, non-aqueous titration can be employed to determine substances poorly soluble in water. The titration end point in non-aqueous media can be found using indicator, potentiometric, conductometric, amperometric, and other techniques.

Another merit of this method is that both colourless and coloured solutions can be titrated. Non-aqueous titration yields more accurate results than the titration of aqueous solutions because owing to the generally low surface tension of organic solvents, the size of drops of non-aqueous liquids is smaller than that of drops of aqueous solutions.

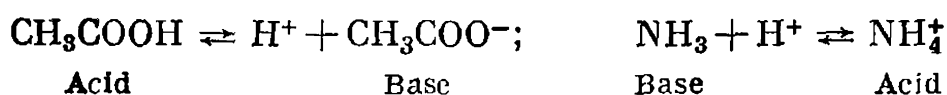
According to the theory of non-aqueous titration, the nature of the solvent and solute determines the interaction between their ions and molecules. The nature of the solvent especially influences the acid-base properties of the solute.

To better understand the theory of non-aqueous titration, we first of all have to define the concepts of an "acid" and a "base".

For a long time, Arrhenius's theory of electrolytic dissociation was predominant. He defined acids as hydrogen-containing compounds that dissociate into hydrogen ions H^+ and anions when dissolved in water, and bases as compounds containing hydroxyl groups that dissociate into hydroxyl ions OH^- and cations when dissolved in water. This theory was found to be inconsistent, however, because many organic compounds exhibit basic properties in reactions, but have no hydroxyl group in their molecules (examples are pyridine, amidopyrine, and alkaloid bases). Similarly, there are substances containing no hydrogen in their molecule, for example aluminium chloride, but in ether this substance reacts with bases and, consequently, exhibits properties of an acid. This phenomenon could not be explained from the standpoints of Arrhenius's theory of electrolytic

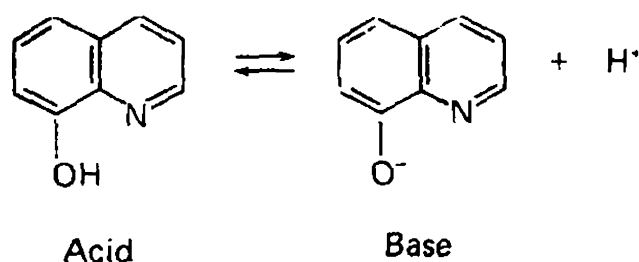
dissociation, and this is why new theories of acids and bases appeared. The most acceptable of them for application in analytical chemistry was the Brönsted-Lowry proton (protolytic) theory.

The Danish scientist V. Brönsted and the British chemist T. Lowry independently defined an acid and a base from the standpoints of the proton theory. By this theory, an acid is any substance that tends to give up a proton H^+ (a proton donor), while a base is any substance that tends to accept a proton (a proton acceptor). For example:

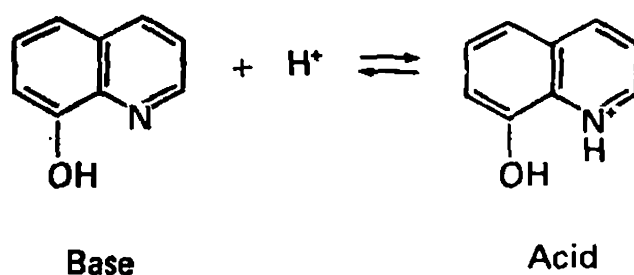


The donating of a proton by an acid or the accepting of a proton by a base is a reversible process.

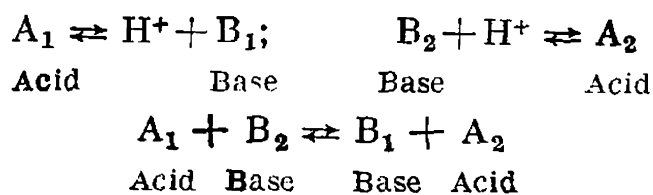
8-Hydroxyquinoline can be considered as an acid:



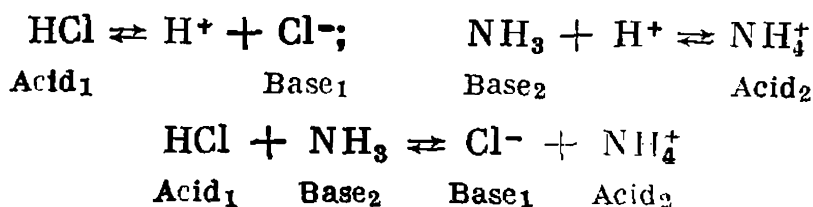
and as a base:



But free protons cannot exist in solutions, they only migrate from an acid to a base capable of accepting them. This is why two processes always occur in a solution, namely,

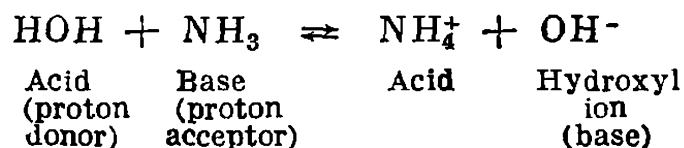


For example:

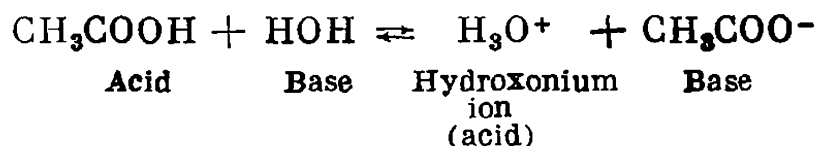


Hence, every acid has a **conjugate base**, and every base has a **conjugate acid**.

There are substances (or ions) that exhibit properties of acids in one solvent and properties of bases in another one. Such a dual (**amphoteric**, or **amphiprotic**) nature is exhibited, for example, by water. In the presence of liquid ammonia it is an acid, because a substance (NH_3) is involved in the reaction that can accept a proton, and water donates it:



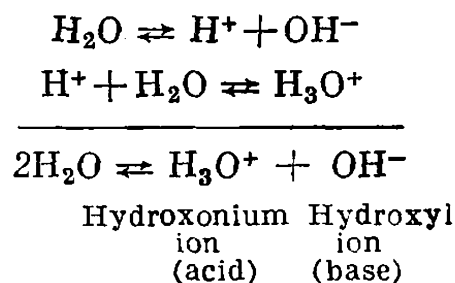
In a reaction with acetic acid CH_3COOH , water acts as a base because the acetic acid donates a proton H^+ that is accepted by the water, which transforms into a hydroxonium ion (an acid):



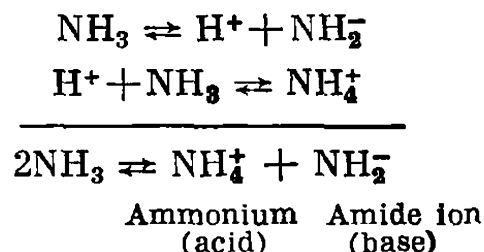
Consequently, the acidity or basicity of a definite substance changes depending on the basicity or acidity of the medium.

According to the Brönsted-Lowry protolytic theory, a neutralization reaction is considered as the transition of a proton from an acid to a base. Such reactions are called **protolysis reactions**. They are of great help for understanding the processes occurring in non-aqueous media.

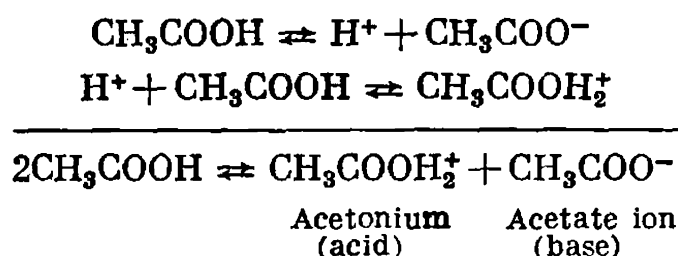
Both organic and inorganic solvents can dissociate into ions like water can. Here the hydrogen ions (protons) combine with the solvent molecules to form complex ions of hydroxonium, ammonium, acetonium, and the like. For example:



Liquid ammonia dissociates to form ammonium ions and amide ions:



Anhydrous acetic acid yields acetonium and acetate ions when it dissociates:



Consequently, the acidity in an aqueous solution is due to hydroxonium ions H_3O^+ , in liquid ammonia to ammonium ions NH_4^+ , and in anhydrous acetic acid to acetonium ions $\text{CH}_3\text{COOH}_2^+$.

Alkalinity in an aqueous solution is due to hydroxyl ions OH^- , in liquid ammonia to amide ions NH_2^- , and in anhydrous acetic acid to acetate ions CH_3COO^- . Thus, the Brönsted-Lowry theory changed the old notions of acids and bases.

By this theory, acids also include many ions capable of donating protons (H_3O^+ , NH_4^+ , $\text{CH}_3\text{COOH}_2^+$, etc.). The range of substances classified as bases has also extended. In addition to substances containing hydroxyl ions OH^- , many substances and ions capable of accepting protons (NH_3 , Cl^- , CH_3COO^- , etc.) are considered to be bases.

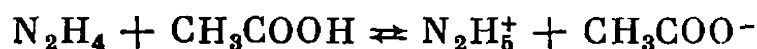
G. Lewis advanced a still more general view of acids and bases. He defined an acid as an acceptor and a base as a donor of an electron pair. These ideas can be helpful in explaining the mechanisms of organic reactions, but are too broad for useful applications in analytical chemistry.

The behaviour of a solute in a non-aqueous solvent depends primarily on the solute's properties. As indicated above, some compounds behave like a base in one medium and like an acid in another one. At the same time, the behaviour of a substance in a solution also depends on the properties of the solvent.

In non-aqueous solvents, the acidity, basicity, and solubility increase. This makes it possible to use acid-base titration for weak acids and bases that are difficult or impossible to analyse in an aqueous medium.

The theory of acids and bases for non-aqueous media was worked out by Franklin and further developed by the Soviet scientists A. Shatenstein, M. Usanovich, N. Izmailov, and A. Kreshkov. A variety of acidic or basic solvents can be used for non-aqueous titration.

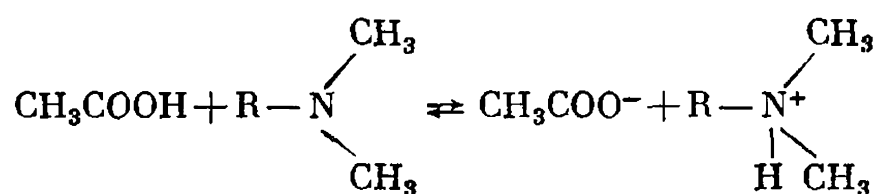
1. Examples of basic (protophilic) solvents are liquid ammonia NH_3 , ethylenediamine $\text{NH}_2(\text{CH}_2)_2\text{NH}_2$, hydrazine NH_2NH_2 and its derivatives, dimethylformamide $\text{HCON}(\text{CH}_3)_2$, and cyclic nitrogen-containing substances such as pyridine $\text{C}_5\text{H}_5\text{N}$. These solvents have a high affinity to a proton and can readily accept it:



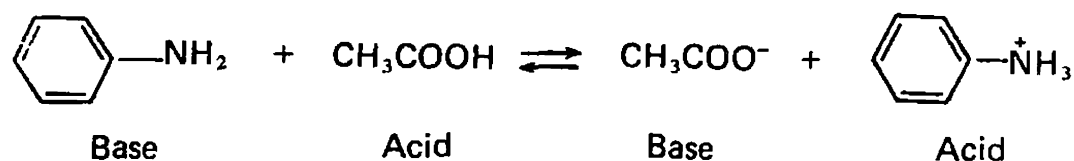
Weak acids, enols, acidic forms of barbiturates and sulphonylamides, and phenols are easily titrated in a medium of basic solvents. The acidity of these compounds in the given solvents increases, and the results of titration are thus more precise. The stronger the basic properties of a solvent, the greater is its effect on weak acids, i.e. the more does it increase the acidic properties of a substance.

2. Acid (protogenic) solvents include hydrogen fluoride HF, sulphuric acid H_2SO_4 , formic acid HCOOH , and acetic acid CH_3COOH (anhydrous).

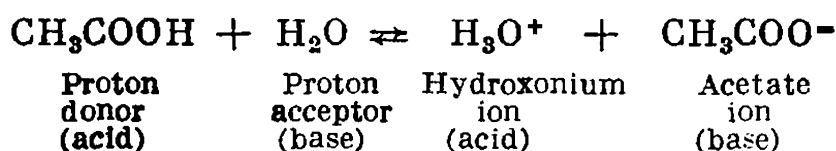
The molecules of protogenic solvents readily donate protons and transform into bases:



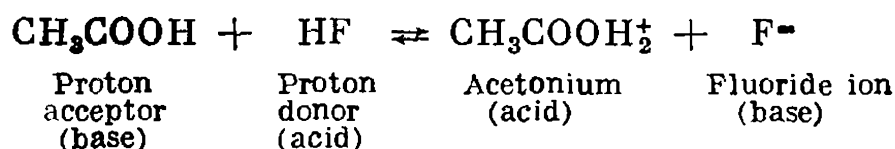
The stronger the acidic properties of solvents, the greater is their effect on weak bases. For example, aniline, which is a very weak base in water, exhibits strong basic properties in anhydrous acetic acid and can be determined by the neutralization method:



But the division of solvents into protophilic and protogenic ones is relative. For example, acetic acid is a proton donor, i.e. an acid, in an aqueous solution:

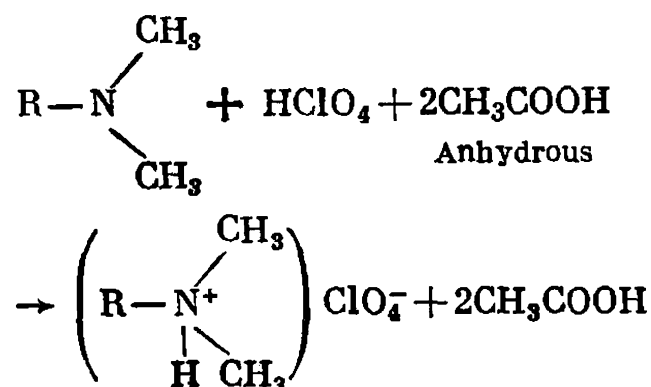


but in liquid hydrogen fluoride it acts as a proton acceptor and is therefore a base:

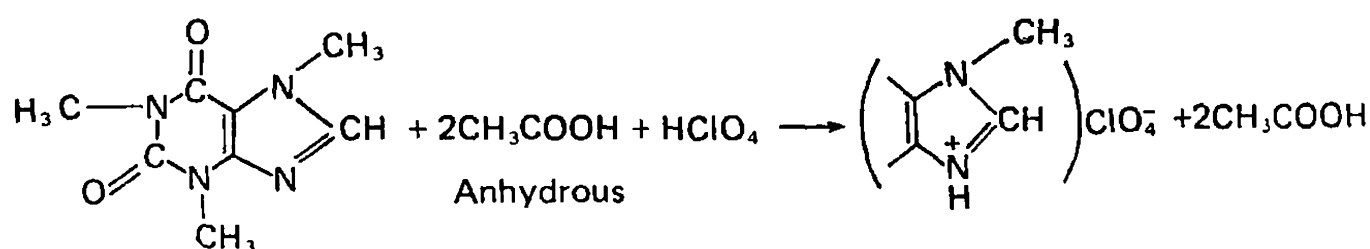


Consequently, the behaviour of a substance in a solution is determined by its affinity to a proton. When two compounds interact, the one that exhibits a lower affinity to a proton, i.e. retains a proton less strongly, is an acid, whereas the one with the higher affinity to a proton is a base.

The overall reaction is

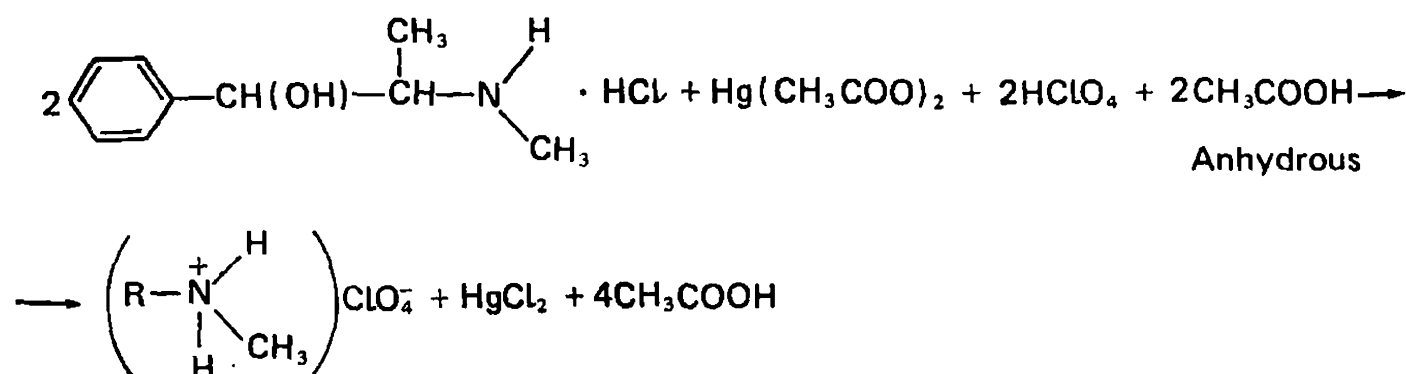


For *caffeine*, we have:



Titration of salts of nitrogen-containing bases and hydrogen halide acids. This group includes most alkaloid salts (papaverine hydrochloride, morphine hydrochloride, homatropine hydrobromide, etc.) and salts of nitrogen-containing heterocyclic bases [dimedrol, sovaine (cinchocaine), quinocide, etc.]. These salts cannot be titrated directly with perchloric acid because the hydrogen halide acids are highly ionized and can affect the change of the indicator's colour at the equivalence point.

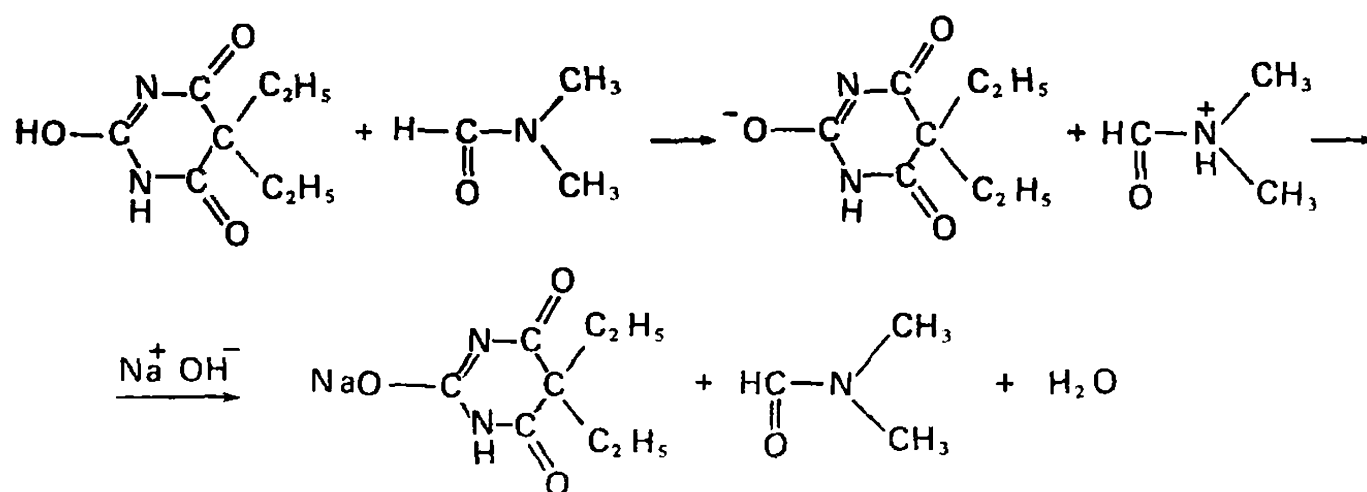
To eliminate the interference of the ionized acid halogen (Cl^- , Br^-), the salts of hydrogen halide acids are titrated in the presence of mercury(II) acetate. As a result, the halogen ion combines into a weakly dissociating compound, i.e. mercury dichloride HgCl_2 or dibromide HgBr_2 , and titration yields good results (R is the residue of an ephedrine molecule):



Titration of weak acids (acid forms of barbiturates, sulphonylamides, and the like). Drugs that are weak acids are titrated in protophilic (basic) solvents which increase the acidic properties of the

weak acids. Dimethylformamide is employed most often for this purpose because it is a good solvent of most organic drugs. This is why dimethylformamide has been adopted officially for the titration of weak acids.

Barbital (barbitone). Dimethylformamide is used as the non-aqueous solvent, a 0.1 *N* solution of sodium hydroxide in a mixture of methanol and benzene or a 0.1 *N* solution of sodium methylate CH_3ONa in a mixture of benzene and methanol as the titrant, and thymol blue as the indicator:



The other acid forms of barbiturates (phenobarbital, hexobarbital, benzonal or benzobarbital, etc.) are determined similarly.

1.3. EXPRESS ANALYSIS

The volume of work of the analytical cabinets of pharmacies is exceedingly great, and if account is taken of the fact that in many countries (including the USSR) all the drugs without fail prepared at a pharmacy must be controlled in various ways, it is essential that drugs at pharmacies be analysed rapidly. The methods of analysis must be simple, require no intricate equipment, and the amount of a drug and the relevant reagents must be minimal (0.5-2 ml of a liquid medicinal form or 0.05-0.1 g of a powder) so that the drug does not have to be prepared again for dispensing. These requirements are met by chemical express analysis, which occupies the leading place among the kinds of control used at pharmacies.

Qualitative express analysis is performed by the semimicro-method in a small porcelain bowl, on a slide, or on filter paper. The latter is placed on a glass plate, a solution of the substance to be analysed is drawn into a capillary or pipette and let out onto the paper. Another, larger pipette is used to drop the required reagent onto the centre of the formed spot of the substance, and a colour thus appears on the filter paper (the product of the reaction of the analyte and the reagent) that tells us whether the composition of the substance is what we expected.

When employing strong acids and alkalies, conduct the reactions on a slide because these substances decompose paper. Quite often filter paper impregnated with the relevant reagents and dried is used for qualitative analysis. For example, paper impregnated with a copper sulphate solution is used to identify sulphonylamide preparations, carboxylic acids, and barbiturates.

Quantitative express analysis uses volumetric methods that ensure sufficient accuracy, simplicity, and rapidity of performance.

When analysing powders, weigh 0.05-0.1 g of the powder on a manually operated balance to ensure that 1-2 ml of the titrant solution will be used for titration.

When analysing liquids, add one or two drops of the indicator to 1-2 ml of the test solution and titrate with a 0.1 or 0.05 *N* solution of the relevant titrant.

When analysing concentrated solutions, the titration of 1 ml would require a comparatively large amount of the titrant solution, therefore concentrated solutions are preliminarily diluted. Mixtures in which the concentration of the ingredient being analysed does not exceed 4% are customarily not diluted.

For the quantitative determination of the ingredients in ointments, take a sample on parchment paper and put it into a flask. Add 3-5 ml of an alcohol or ether. After the ointment base dissolves, titrate the solution.

Several working formulas are used to process the results of analysis depending on what is required. The following notation is used in these formulas: *V* is the volume of a solution in millilitres (ml), *a* is the mass of a preparation in grammes (g) or its volume in ml, *K* is a correction factor to the standard (titrant) solution, and *T* is the titre of the standard solution with respect to the solution being determined in g/ml.

The following working formulas are used the most:

(1) the content of a substance in per cent (*X*) in a powder or ointment is

$$X = \frac{VKT}{a} \times 100\% \quad (1.1)$$

where *V* is the volume of the standard solution of a definite normality, ml, and *a* is the mass of the preparation, g;

(2) the content of a substance in per cent in a solution is also calculated by formula (1.1), but in this case *a* is the volume of the preparation taken for the determination, ml;

(3) if during analysis a part of a preparation is diluted to an exact volume and an aliquot (exact) part of the dilute solution is taken for the determination, the content of a substance in per cent is

$$X = \frac{VKT V_1}{a V_2} \times 100\% \quad (1.2)$$

where V_1 is the volume of the diluted solution of the preparation, ml, and V_2 is the volume of the aliquot part of this solution taken for the determination, ml;

(4) the content of a substance in grammes in powders, tablets, or mixtures is

$$X = \frac{VK Tb}{a} \quad (1.3)$$

where b is the mass of one powder or one tablet, g, or the total volume of the mixture, ml;

(5) if back-titration is used in analysis, the content of a substance is also calculated by formulas (1.1)-(1.3), but instead of V the quantity V' is introduced into them. It is found by the expression:

$$V' = V_0 K_0 - VK \quad (1.4)$$

where V_0 is the volume of the main standard solution reacting with the substance being determined, ml, V is the volume of the auxiliary standard solution used to titrate the excess of the main solution, ml, K_0 and K are the correction factors of the main and auxiliary standard solutions, respectively.

Microburette. A microburette (Fig. 1) is used in titration by the express method for delivering an exact volume of a liquid.

Procedure. Preliminary fill the microburette and the bent capillary tube with the titrant solution. To do this, close the cock and compress the rubber bulb with your left hand, close the opening for air in the bulb with your forefinger, open the cock with your right hand, gradually release the bulb and suck the titrant solution into the microburette up to about two-thirds of its volume. Close the cock, turn the rubber tubing upward, and press the rubber tubing of the valve to let the solution past the bead into the capillary tube until the latter is filled. See that there is no air in the capillary.

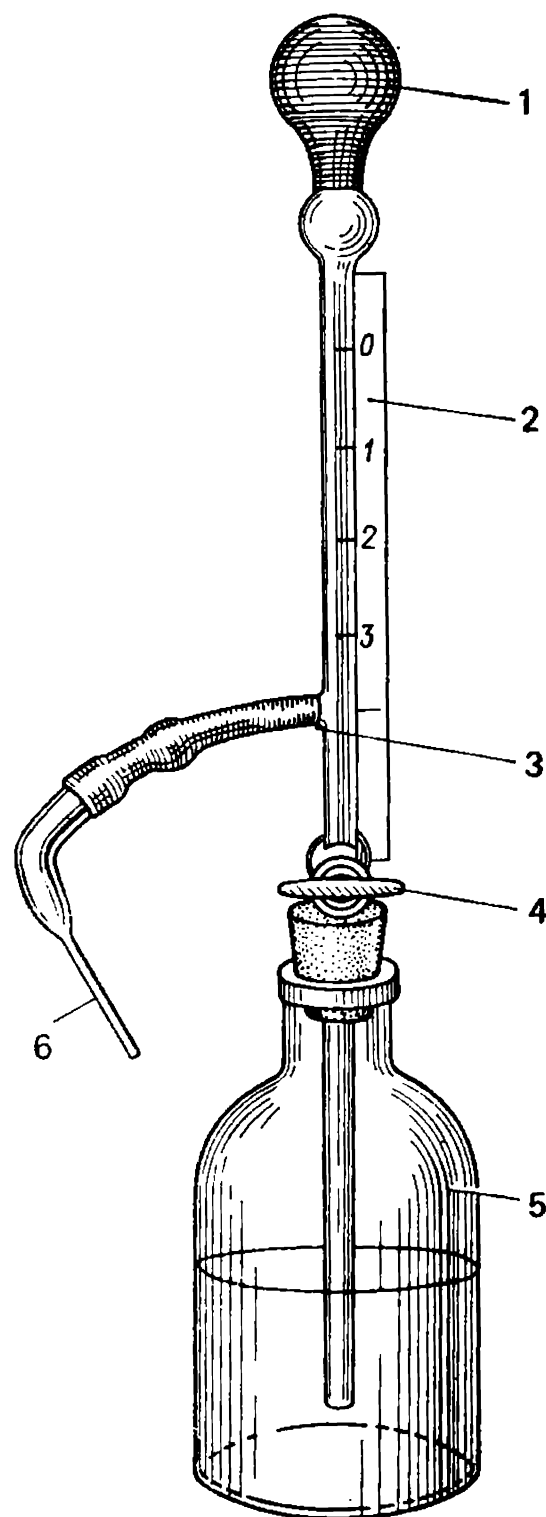


Figure 1. Microburette:

1—rubber bulb; 2—graduated tube for 3 ml; 3—rubber tubing with a glass bead inside; 4—cock; 5—vessel; 6—capillary tube

If the solution flows into the capillary poorly, compress the rubber bulb while deforming the rubber tubing.

Adjust the level up to the zero mark. To do this, return the pipette to its initial position, open the cock, and use the rubber bulb as above to suck the titrant solution into the burette. Close the cock after releasing the excess solution back into the feeding vessel, and the microburette is ready for work.

The following rules must be observed for the convenient and rapid filling of a burette:

(a) the rubber bulb should have a small opening for the inlet and outlet of air;

(b) do not compress and release the bulb sharply, because otherwise the solution will get into it, during titration the solution will enter the burette, and accurate titration will be impossible;

(c) if the titrant solution does get into the bulb, remove the burette from the vessel, and compress and release the rubber bulb several times until all the liquid is forced out of it;

(d) to prevent air from getting into the bent capillary tube, press the rubber tubing only near the bead;

(e) to prevent a reduction of the pressure in the vessel with the titrant solution, periodically remove the burette from the vessel.

Chapter 2. Physicochemical Methods

The number of new drugs is constantly growing. This requires new methods for controlling their quality.

Modern pharmaceutical analysis must meet the following requirements:

(1) the analysis should take a minimal time;

(2) the accuracy of the analysis should meet the demands of the State Pharmacopoeia;

(3) the analysis should be performed with a minimal amount of the analyte and reagents.

These requirements are met by the physicochemical methods of analysis, a merit of which is their universal nature—they can be employed for analysing organic compounds with a diverse chemical structure.

2.1. OPTICAL METHODS

REFRACTOMETRY

Refractometry is one of the simplest physicochemical methods of analysis. It requires very small amounts of the analyte and is performed during a very short time. In pharmaceutical analysis, it is

used for identifying drugs, establishing their purity, and for quantitative determinations.

The refractometric method of analysis is based on measuring the refractive index of the analyte. The refractive index is one of the fundamental physical properties of a substance, namely, a pure substance is characterized by a definite refractive index. When a ray of light travels from one transparent medium into another one, its direction changes at the interface—the ray is refracted.

The ratio of the speed of light in the air (v_1) to the speed of light in the substance being tested (v_2), equal to the ratio of the sine of the angle of incidence of the light ray (α) to the sine of the angle of its refraction (β), is called the **refractive index** (n) and is a constant for a given wavelength of the light ray:

$$n = \frac{v_1}{v_2} = \frac{\sin \alpha}{\sin \beta} \quad (2.1)$$

The value of the refractive index depends on the nature of a substance, the wavelength of the light, the concentration of the solution, and the temperature.

The refractive index is measured by a special instrument known as a **refractometer**. A variety of these instruments are available on the market such as the laboratory one RL and the universal one RLU.

The refractive index is customarily measured at 20 °C and a wavelength of 589.3 nm of the sodium spectrum D line (n_D^{20}). The limits of measuring the refractive index in this case are 1.3 to 1.7.

A refractometer determines the refractive index by the critical angle method (the critical angle is the limiting angle of incidence in a denser medium that results in an angle of refraction of 90°; at larger angles of incidence total internal reflection occurs). A schematic view of an arrangement used for this purpose is shown in Fig. 2.

Design of a refractometer (Fig. 3). The main component of a refractometer is a measuring prism made from optical glass whose refractive index is known. The entrance face of the measuring prism in contact with the analyte is the interface at which refraction and total internal reflection of a ray occur. The refraction or reflection of the light is observed in the instrument eyepiece.

Procedure. 1. Before beginning measurements, see that the contacting prism surfaces are clean.

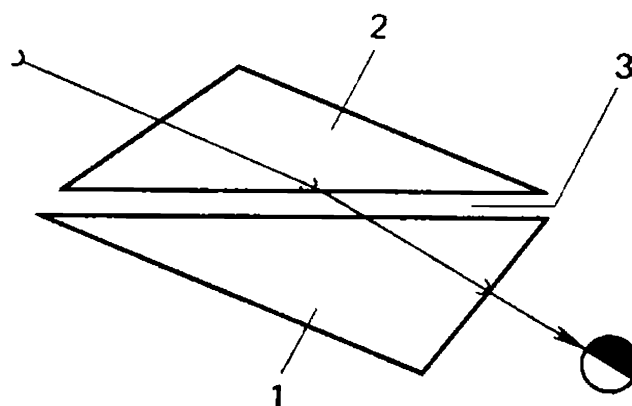
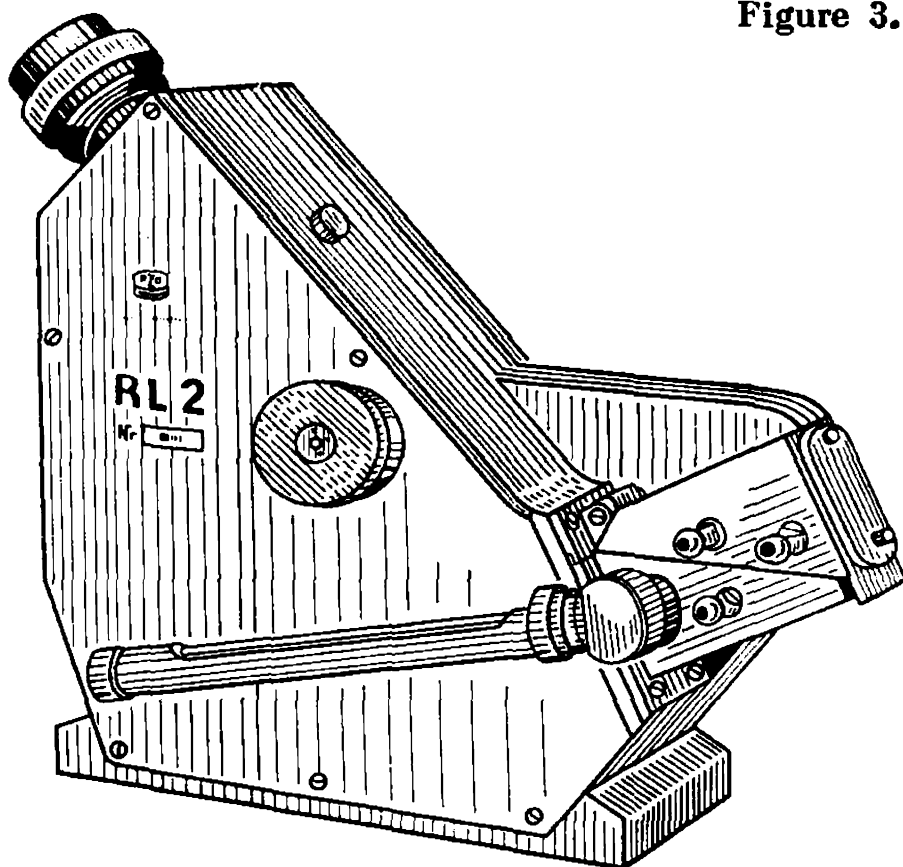


Figure 2. Determination of the refractive index:

1—measuring prism; 2—illuminating prism; 3—substance being studied

Figure 3. Refractometer



2. Check the zero point. Apply two or three drops of distilled water to the surface of the measuring prism, and carefully cover them with the illuminating prism. Open the illuminating window and set it in the direction of the maximum intensity of the light source with the aid of mirrors. By rotating the screws, obtain a sharp boundary between the light and dark fields in the field of vision of the eyepiece. By rotating the relevant screw, make the boundary between the light and shadow exactly coincide with the point of intersection of the lines in the upper window of the eyepiece. The vertical line in the lower eyepiece window indicates the result of measurement, namely, the refractive index of water at 20 °C equal to 1.333. If the reading differs from this value, set the refractive index by manipulating the relevant screw to 1.333, and use a cap key (remove the adjusting screw) to bring the light and shadow boundary to the point of intersection of the lines.

3. After setting the instrument at its zero point, lift the chamber of the illuminating prism, and remove the water with filter paper, a gauze or flannel napkin. Next apply one or two drops of the solution to be studied onto the plane of the measuring prism and close the chamber. Rotate the screws until the light and shadow boundary coincides with the point of intersection of the lines. Read the refractive index of the solution on the scale in the bottom window of the eyepiece. The concentration of the solution is determined from the relevant tables. Use a different table when measuring the concentration of solutions whose temperature differs from 20 °C.

4. After each determination, rinse both chambers with water and wipe them with filter paper or a napkin. Place a thin layer of cotton wool between the chambers.

There are tables for determining the concentration of drugs prepared by the gravimetric or gravimetric-volumetric method. These tables list the refractive indices and the concentrations of substances corresponding to them. Some tables give the refractive indices with an accuracy up to the third digit after the decimal point. In this case, the concentration corresponding to the value of the refractive index taken with a fourth digit is determined by interpolation.

Example. The refractive index of a calcium chloride solution is 1.3453. The closest values in a table are 1.345 and 1.346, the relevant concentrations are 10% and 10.9%, and the difference between them (0.9%) equals unity of the third digit after the decimal point. Hence the concentration of the tested solution is

$$10 + \frac{(1.3453 - 1.345)(10.9 - 10)}{(1.346 - 1.345)} = 10.27\%$$

Notes. The prisms in an instrument fail the most rapidly, therefore the following precautions must be observed when working with them:

(1) before determining a refractive index, thoroughly clean the prisms;

(2) never measure the refractive indices of acids and alkalies because they corrode the prism surfaces;

(3) after measurements, wipe the prism surfaces with a clean soft napkin wetted with water or alcohol, wipe them dry, and place a small, dry, and clean napkin or cotton wool between the prisms;

(4) it is strictly prohibited to rotate the screw coloured red and leave the analyte liquid for a long time between the prisms, especially a calcium chloride solution, because the surfaces of the prisms after this become coated with a thin dull layer, and it becomes impossible to measure the refractive index.

POLARIMETRY

The polarimetric method of analysis is based on the ability of substances to rotate the plane of polarization when polarized light passes through them. Substances rotating the plane of polarization of light to the right or left are called optically active.

If the plane of polarization rotates to the right (clockwise), the substance is said to be **dextrorotatory** (from the Latin *dexter*—right), and its name is preceded by the prefix sign (+) or the letter d; if the plane of polarization rotates to the left (anticlockwise), the substance is said to be **levorotatory** (from the Latin *laevus*—left), and its name is preceded by the prefix sign (—) or the letter l.

The deflection of the plane of polarization from the initial position expressed in angular degrees is called the **angle of rotation** and is designated by the Greek letter α . The angle of rotation depends on the nature of the optically active substance, its layer thickness, temperature, the nature of the solvent, and the wavelength of the light. The optical rotation is generally determined at 20 °C and at the wavelength of the sodium spectrum D line (589.3 nm).

The optical activity of a substance is characterized by the **specific rotation**, i.e. the rotation of the plane of polarization produced by a layer of the substance 1 dm thick at a concentration of 1 g/ml at 20 °C. The specific rotation of solutions is evaluated by the formula

$$[\alpha]_D^{20} = \frac{\alpha \times 100}{lC} \quad (2.2)$$

where α is the measured angle of rotation, deg, l is the thickness of the solution layer, dm, and C is the concentration of the solution, %.

Knowing the specific rotation of a substance, which is constant within a definite interval of concentrations, we can calculate its content (C) in the solution in per cent by the formula

$$C = \frac{\alpha \times 100}{[\alpha]_D^{20} l} \quad (2.3)$$

For liquid substances, the specific rotation is

$$[\alpha]_D^{20} = \frac{\alpha}{l\rho} \quad (2.4)$$

where ρ is the density of the liquid, g/cm³.

Polarimetry is widely employed in pharmaceutical analysis to establish the optical activity of drugs, their quality and content.

Instruments known as **polarimeters** are used to measure the angle of rotation of the plane of polarization. A variety of polarimeters are available, but their principle of operation is the same. The design of a polarimeter is shown in Fig. 4.

Optical system of instrument. Light from the source passes through a light filter (or ground glass) to the polarizer prism that divides it into two equal polarized beams. The polarizer is arranged so that the planes of polarization of both beams make the same angle with the plane of polarization of the analyzer. If a tube with a sample solution is placed in the paths of both beams, the planes of polarization will be rotated, and one of the beams will be attenuated more by the analyser than the other one. By rotating the compensator, one can compensate this change in the flux. Simultaneously, the scale rotates, which is illuminated through a prism and is observed through a magnifying glass. The eyepiece is used to observe the colour of the fields.

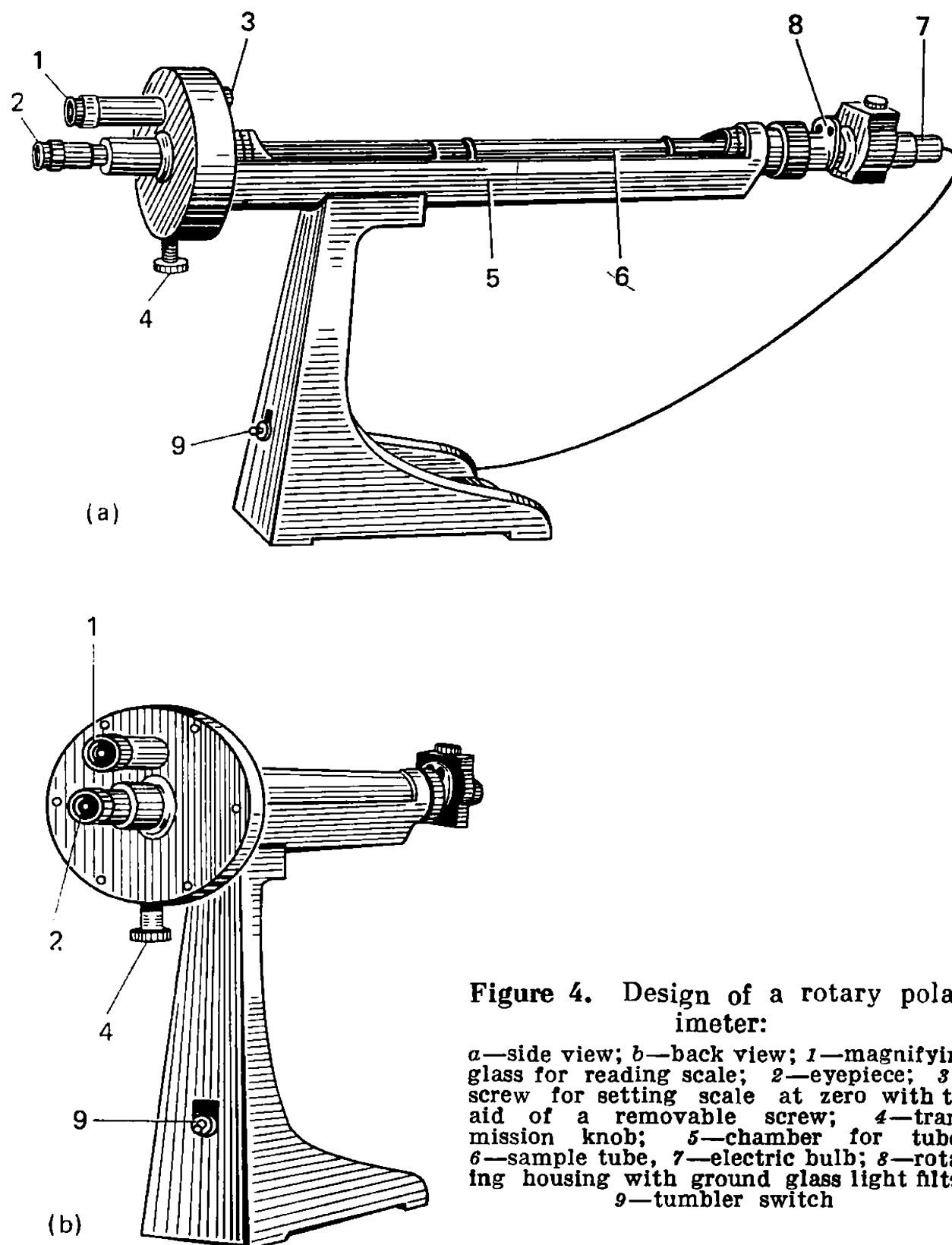


Figure 4. Design of a rotary polarimeter:

a—side view; *b*—back view; 1—magnifying glass for reading scale; 2—eyepiece; 3—screw for setting scale at zero with the aid of a removable screw; 4—transmission knob; 5—chamber for tubes; 6—sample tube; 7—electric bulb; 8—rotating housing with ground glass light filter; 9—tumbler switch

Procedure. 1. Set the eyepiece and the magnifying glass of the scale (by rotating their mounts) to the maximum sharpness of the image so that the vertical line dividing the field of vision into two halves is clearly seen, while the graduations and figures of the lower scale and vernier (upper scale) are clearly seen in the field of vision of the magnifying glass.

2. Set the instrument at zero. To do this, equalize the intensities of illumination of both halves of the field of vision by means of the

transmission knob. The zeros of the scale and the vernier must coincide. Otherwise use a cap key to shift the vernier until its zero coincides with that of the scale.

3. Rinse the sample tube twice with the analyte solution. Next fill it, pouring in the liquid until its meniscus protrudes above the edges of the tube. Wait a while for any gas present to bubble out. Smoothly cover the tube with a clean piece of glass using a sliding motion to remove the excess liquid.

4. Put the tube with the analyte solution into the chamber of the instrument. The illumination intensities of both halves of the field of vision will be different. Rotate the transmission knob to equalize them.

5. Take the reading with an accuracy up to 0.01.

6. Again equalize the illumination of both halves of the field and take readings, repeating this five times. Take the mean value of the readings as the result.

Choice of Light Filter. 1. If colourless or slightly coloured test solutions give no difference in the illumination intensity of the two halves of the field, introduce the ground glass into the optical system.

2. If the polarization of colourless or slightly coloured solutions gives a certain difference in the intensities of the two halves of the field and they cannot be equalized, introduce a light filter into the optical system.

3. When working with darkly coloured solutions, place the rotating housing in its position corresponding to the maximum illumination of the field of vision. Do not introduce the ground glass or the light filter.

FLUOROMETRY

The fluorescence method of analysis is based on studying the emission spectra of the analytes. This method is employed both for identifying substances according to the colour of their luminescent emission and for quantitative analysis according to the intensity of the luminescence measured by special instruments.

In an experiment, the fluorescence of many substances is caused by ultraviolet irradiation. For example, molecules of caffeine and nicotine in ultraviolet light have a violet fluorescence, papaverine, sovcaïn (cinchocaine), and barbamył (amobarbital)—a light blue one, codeine and no-spa (drotaverine)—a yellow one, and reserpine and cotarnine hydrochloride—a yellow green fluorescence. This property is used for identification of the drugs.

In the State Pharmacopoeia, the colour of the fluorescence of many drugs is indicated as a way of identifying them. Examples are dimit-hine, methylthiouracil, progesterone, reserpine, riboflavin, and quinine hydrochloride.

The intensity of fluorescence is affected by the concentration of the substance in the solution, the nature of the solvent, the temperature, the pH of the medium, and the presence of foreign substances. Fluorescence is generally determined in solutions with a solute concentration not exceeding 10^{-4} to 10^{-5} g/ml.

An increase in the concentration of the fluorescing substance results in reduction or complete disappearance (extinction) of the fluorescence. Extinction of the fluorescence can also be due to other causes such as a chemical reaction of foreign substances with the fluorescing substance that yields non-fluorescing products.

Some medicinal agents do not fluoresce by themselves, but can be converted chemically into substances that do fluoresce. For example, thiamine (aneurine) and cocarboxylase (thiamine pyrophosphate) react with potassium ferricyanide in an alkaline solution to form thiochrome, and the latter when irradiated by ultraviolet light exhibits a light blue fluorescence. Adrenaline (epinephrine) and folic acid (folacin) as a result of chemical transformations produce fluorescing substances used to identify them.

The quantity of an analyte is determined with the aid of an instrument known as a fluorometer by comparing the intensity of fluorescence of the analyte solution with that of a standard solution. The test is conducted under identical conditions with the pure solvent.

The content of the pure substance (X) in the preparation is

$$X = \frac{(n - n_2) C}{(n_1 - n_2)} \quad (2.5)$$

where C is the concentration of the standard solution, n is the reading of the fluorometer for the analyte solution, n_1 is the same for the standard solution, and n_2 is the same for the reference solution (pure solvent).

Since the intensity of fluorescence is directly proportional to the concentration of a substance within a very narrow region, the ratio $(n - n_2)/(n_1 - n_2)$ should be at least 0.4 and at most 2.50. The relative error of fluorometric analysis is 2-5%.

PHOTOMETRY

Photometric (absorption) methods of analysis are based on the ability of an analyte to selectively absorb light. The analysis of substances based on the measurement of light absorption includes spectroscopy and photolorimetry.

Spectroscopy is based on the absorption of monochromatic light, i.e. light of a definite wavelength (0.2-20 μm) in the visible, ultraviolet, and infrared regions of the spectrum. A variety of spectrometers and spectrophotometers are employed for the light absorption

measurements. They always use monochromatic light obtained with the aid of an optical system known as a monochromator.

Absorption in the ultraviolet and visible regions of the spectrum is associated chiefly with the excitation of electrons. The absorption of light in the infrared region of the spectrum is due to molecular vibrations.

Depending on the range of wavelengths used, we distinguish spectroscopy in the ultraviolet region with a wavelength range of 200-400 nm, in the visible region of the spectrum (400-760 nm), and in the infrared region (760-20 000 nm). But the unit used for measuring the wavelength of infrared spectra is generally the micrometre ($1\ \mu\text{m} = 10^{-4}\ \text{cm} = 10^3\ \text{nm}$) or the wave number ν (cm^{-1}), i.e. the number of waves per centimetre.

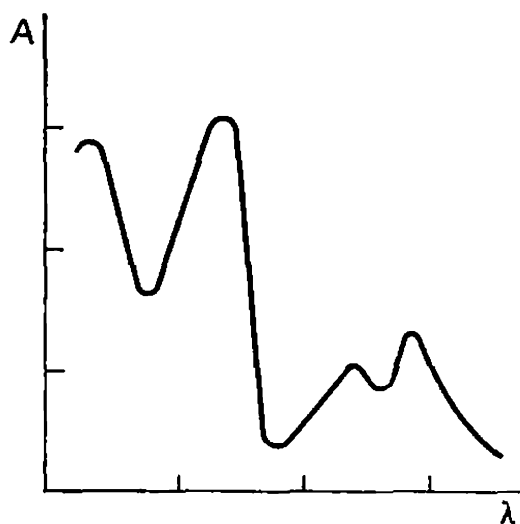


Figure 5. Absorption spectrum of riboflavin

Spectroscopy in the ultraviolet and visible regions of the spectrum is employed more frequently in pharmaceutical analysis. The method of ultraviolet spectroscopy has been included in the State Phar-

macopoeia, the International Pharmacopoeia, and also in the latest editions of the pharmacopoeiae of almost all countries for the identification, qualitative, and quantitative determination of a substance in a drug.

An absorption spectrum is a graphical representation of the amount of light absorbed by a substance at definite wavelengths. To plot a characteristic absorption curve, the values of the wavelengths (λ) in ultraviolet spectroscopy or of the wave numbers (ν) in infrared spectroscopy are laid off along the axis of abscissas, and the value of the absorbance (A), previously known as the optical density, or the per cent transmittance (T) (in infrared spectroscopy) along the axis of ordinates (Figs. 5, 6).

When plotting the curves of absorption spectra in the ultraviolet and visible parts of the spectrum, the values of the absorptivity (extinction coefficient) a or the molar absorptivity ϵ can be used. Here a is the absorption of a solution containing one gramme of a substance in 100 ml of its solution at a layer thickness of one centimetre, and ϵ is the absorption of a 1 M solution of a substance at a layer thickness of one centimetre. These quantities are determined experimentally and are listed in various tables in the literature for specified wavelengths.

A characteristic of an absorption spectrum is a position of the

peaks (minima) of light absorption by the substance, and also the intensity of absorption, which is determined by the optical density D or absorptivity a at definite wavelengths.

Ultraviolet spectroscopic measurements are generally conducted in solutions. The solvents used are distilled water, acids, alkalies, alcohols (ethanol, methanol), and some other organic solvents. The solvent and the analyte must not absorb light in the same region of the spectrum. The form of the latter can change in various solvents, and also when the pH of the medium changes.

The absorption of light by analytes is due to the presence in their molecules of **chromophores**, which are specific portions of

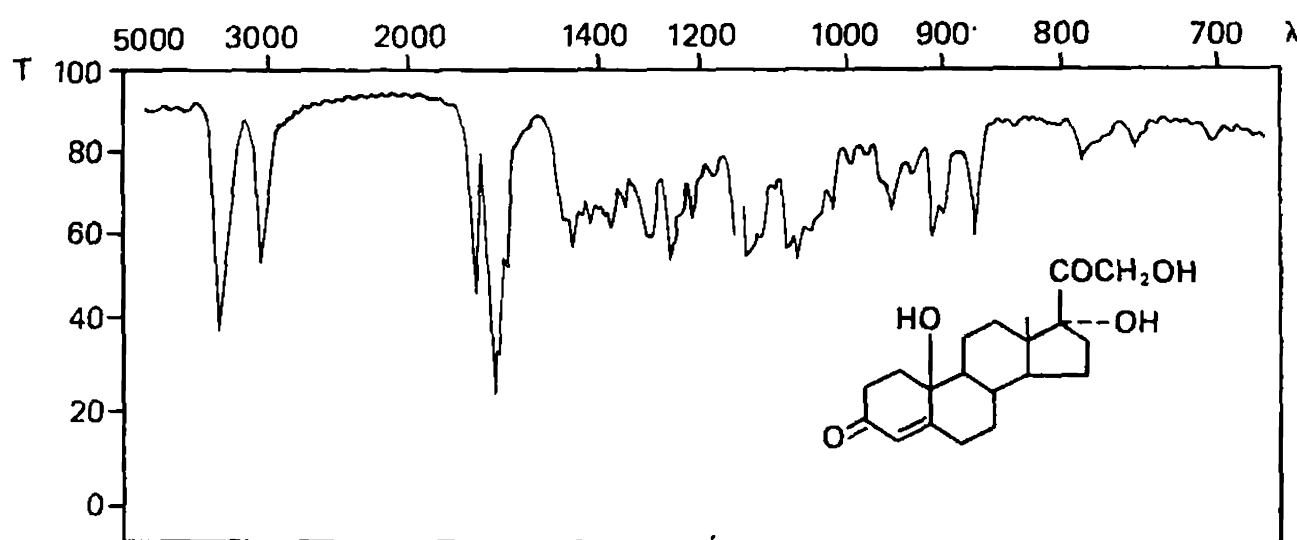


Figure 6. Infrared spectrum of hydrocortisone

molecules that can absorb radiant energy in the visible or ultraviolet region. They include $-\text{C}=\text{C}-$, $-\text{C}\equiv\text{C}-$, $-\text{COOH}$, $-\text{C}=\text{O}$, $=\text{NH}$, $-\text{N}=\text{N}-$, NO , and NO_2 , and other functional groups.

Every functional group in a molecule of a substance is characterized by the absorption of light in a definite region of the spectrum, and this property is used for the identification and quantitative determination of a substance in a drug.

In addition to chromophores, a molecule may contain one or more functional groups that themselves do not absorb in the near ultraviolet region being scanned, but can affect the behaviour of the chromophore they are conjugated with. These groups, called **auxochromes**, usually cause absorption by a chromophore at larger wavelengths and at a higher value of the absorptivity than feature the given chromophore. Examples of auxochromes are $-\text{SH}$, $-\text{NH}_2$, and $-\text{OH}$.

Infrared spectra for most organic compounds, unlike ultraviolet spectra, are characterized by the presence of a large number of absorption peaks (see Fig. 6). This is why infrared spectroscopy provides more complete information on the structure and composi-

tion of the analyte that enables one to identify compounds very close in structure.

In the State and International Pharmacopoeiae, infrared spectroscopy has been adopted for identifying many organic medicinal agents with polyfunctional groups in their molecules by comparing their spectra with those of standard specimens obtained under the same conditions. The infrared spectra of antibiotics, hormones, coumarines, and many other organic medicinal agents are given in recent publications on the subject.

The photolorimetric method of analysis is based on measuring the absorption of non-monochromatic light by coloured compounds in the visible part of the spectrum.

If the analytes are colourless, they are converted into coloured compounds by reaction with a suitable reagent. In this case, the majority of the coloured compounds are complexes or complex ligands. The latter must be stable and have a constant composition and a high colour intensity. Depending on how the concentration of substances in coloured solutions is measured and on the apparatus used, the methods of photolorimetric analysis are divided into visual and photoelectric ones.

In the visual method, called **colorimetry**, the intensity of the colour of the analyte solutions is compared with that of standard solutions in which the concentration of the substance is known.

In the photoelectric methods of analysis, the colour intensity, i.e. the absorbance (A) of the coloured analyte solution is measured by photoelectrocolorimeters (Fig. 7) or spectrophotometers in the visible region of the spectrum.

The photometric methods of analysis (spectroscopy, photolorimetry) are based on the **Bouguer-Lambert-Beer law**, which establishes the relation between the absorption of the analyte solution, the concentration of the analyte in this solution, and the thickness of the absorbing layer.

By this law, the absorbance of a solution is directly proportional to the concentration of the absorbent C , the thickness of the layer b in centimetres, and the molar absorptivity or absorptivity x (in the former case, $x = \varepsilon$, and in the latter, $x = a$). This relation is

$$A = xbC$$

whence

$$C = \frac{A}{xb} \quad (2.6)$$

The fundamental principle of operation of photoelectrocolorimeters consists in that light of a definite interval of wavelengths passes through a cell with a coloured solution or solvent and falls onto a photoelectric cell that transforms the radiant energy into electrical energy measured by a galvanometer.

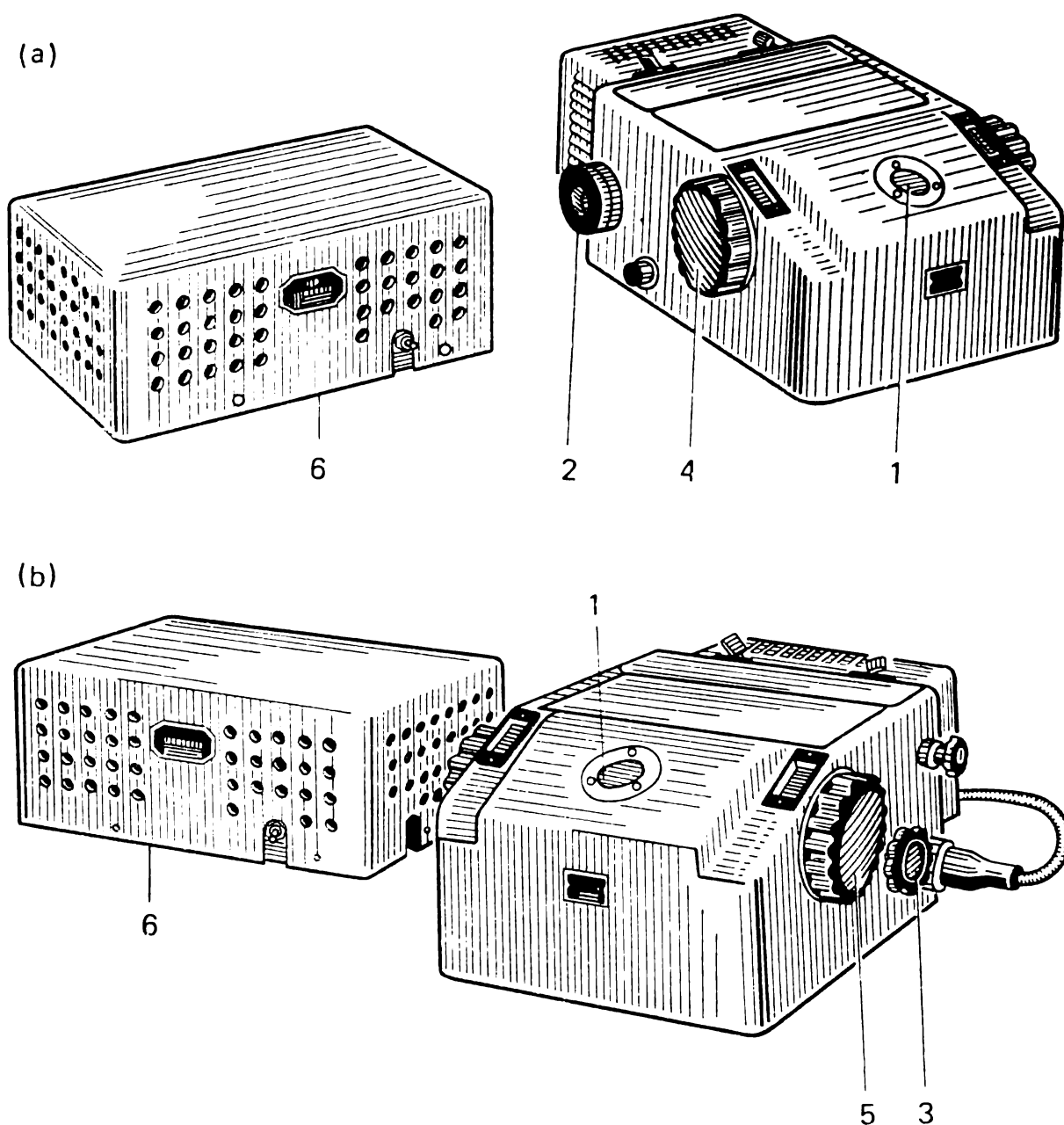


Figure 7. Design of ФЭК-56M photoelectrocolorimeter:

a — left view; *b* — right view; 1 — indicator; 2 — light filter knob; 3 — cell with knob; 4 — left drum; 5 — right drum; 6 — power supply unit

Procedure. 1. Connect the instrument to the mains and let it warm up for 10 min.

2. Introduce a light filter (No. 3).

3. Place the cell with the solvent into the left light beam during the entire period of measurement.

4. Place the cell with the analyte solution into the right light beam.

5. Set the right drum to the graduation 100 of the transmittance scale ($A = 0$).

6. Open the shutter.

7. Rotate the left drum until the light fluxes become equal.

8. Place the cell with the solvent into the right light beam.

9. Rotate the right measuring drum until the light fluxes become equal.

10. Read the value of the transmittance or the absorbance on the scale of the right drum. In the former case, find $A = -\log T$.

11. Find the concentration of the analyte solution from a graph according to the known value of the absorbance.

Determination of the Concentration of a Solution. When determining the concentration of a substance in a solution, proceed as follows:

choose a light filter;

choose a cell (specimen container);

plot a graduation curve for the given substance;

measure the absorbance or transmittance of the analyte solution and determine the concentration of the analyte in it.

Plotting of a Graduation Curve. Take a standard specimen of the given analyte, and prepare a number of solutions of it with known concentrations. Measure the absorbances of all the solutions, and plot the graduation curve by laying off the known concentrations along the axis of abscissas, and the absorbances corresponding to them along the axis of ordinates.

The graduation curve is used to determine the unknown concentration of the analyte in its solutions. To do this, pour a solution into the cell for which the graduation curve was plotted, use the same light filter, and determine the absorbance. Next use the graduation curve to find the concentration corresponding to the measured value of the absorbance. Check the graduation curve from time to time, using a standard specimen for this purpose.

In recent years, pharmaceutical analysis has been characterized by the use of methods such as flame photometry and differential spectrophotometry in the quantitative analysis of drugs. Differential spectrophotometry substantially improves the accuracy of the spectrophotometric and photolorimetric analysis of medicinal agents. This method enables one to determine large amounts of individual components of a mixture because the absorbance of the analyte solution is measured not relative to the pure solvent (or solution of reagents), but relative to a reference solution containing a known amount of the analyte.

2.2. ELECTROCHEMICAL METHODS

POTENTIOMETRY

This method is used to determine the hydrogen ion concentration in a solution (the pH of the medium) and establish the equivalence (end) point of titration when its determination using indicators is hindered for various reasons (for coloured solutions, when the change in the indicator colour at the equivalence point is hardly noticeable,

etc.). Potentiometric titration makes it possible to accurately establish the titration end point by the change in the electrode potential arising between the solution and an electrode immersed in it.

The method is based on the change in the potential of an electrode immersed in an analyte solution and consists in measuring the electromotive force (e.m.f.) between two electrodes. One of them is an **indicator electrode** whose potential depends on the activity of the hydrogen ions in the solution, and the other is a **reference electrode** with a known constant value of its potential. A glass electrode is generally used as the indicator one, and a calomel or silver-silver chloride electrode, as the reference one.

A variety of laboratory pH meters are used for direct measurement of the pH.

POLAROGRAPHY

This method of analysis is based on measuring the current arising in the processes of oxidation or reduction of an analyte on the surface of a microelectrode (the working electrode). The method is used for the qualitative and quantitative assessment of a number of medicinal substances.

2.3. CHROMATOGRAPHIC METHODS

The chromatographic method of analysis was first proposed in 1903 by the Russian scientist M. Tswett. His works were the cornerstone for the further development of chromatography. The latter is one of the sensitive methods of investigation.

Chromatography is a way of separating mixtures into their components that do not change their original properties. The methods of chromatography are classified (1) by the state of aggregation of the mixture that is separated into components (gas, liquid, and gas-liquid); (2) by the separation mechanism (adsorption, partition, ion-exchange, precipitation, etc.); and (3) by the embodiment of the chromatographic process (column, capillary, and surface, i.e. paper and thin-layer).

Thin-layer and paper chromatography have found the greatest application in pharmaceutical analysis*.

THIN-LAYER CHROMATOGRAPHY

Chromatography in a thin sorbent layer (TLC) was used in pharmaceutical analysis for separating extracts and tinctures of medicinal plants by the Soviet scientists N. Izmailov and M. Shraider (1938).

* Since the principle of paper chromatography is similar to that of thin-layer chromatography, we shall omit its description and treat only TLC, which is used the most in pharmaceutical analysis.

TLC is employed to separate mixtures of medicinal agents, identify them, establish their purity, and determine the components quantitatively. A merit of TLC is that it can separate drug mixtures into separate components similar in their chemical structure and properties, for example, mixtures of amino acids, alkaloids, barbiturates, and sulphonylamides.

This method is especially convenient for analysing small amounts of poisonous and highly potent substances in a compound drug when it is difficult to determine them by chemical methods. It is also employed for detecting impurities in a substance, which is especially important in industrial control of the quality of the synthesis intermediates. Another merit of TLC is that it does not require intricate equipment and is therefore accessible for various investigations under any conditions.

TLC is carried out in two ways—with a stationary and a mobile sorbent layer. Over twenty different sorbents are employed, among which the most popular are aluminium oxide, various grades of silica gel, cellulose, polyamide powder, and synthetic resins.

Recent years have seen the widespread introduction of commercially prepared TLC plates with the stationary phase attached (for example, "Silufol" plates produced in Czechoslovakia).

In chromatography, a solution of the analyte or a mixture of substances is applied with a capillary onto a glass plate (6×9 or 12×16 cm in size) with a stationary sorbent layer or onto a "Silufol" plate at the start line. The plate is next placed at an angle into a special chamber (a rectangular glass jar with a ground glass lid) containing a mixture of the relevant solvents. The latter owing to the capillarity of the sorbent layer migrate along the plate, carrying along the substances from the mixture applied at the start line over different distances. After the solvent has risen to a definite height, the plate is extracted from the chamber, dried, and developed using the relevant chemical reagents.

The substances on a chromatogram can also be detected by their fluorescence in ultraviolet light (ultraviolet lamps of various systems are used).

The position of the spots of the substances after chromatography is characterized by the value of the retardation factor (or front ratio) R_f :

$$R_f = \frac{AC}{AB} \quad (2.7)$$

where AC is the distance from the start line to the centre of the spot, and AB is the distance from the start line to the solvent front (Fig. 8).

The value of R_f for each substance is quite definite and is a characteristic value. The values of R_f are used to identify the substances

in a mixture. Since the value of R_f depends substantially on the quality of the sorbents, the purity of the solvents, the temperature, the amount of substance in the chambers, and other factors, the reliability of analysis is improved by using reference solutions of the same substances. These solutions are applied to the start line of the plate next to the analyte mixture. Identification is considered to be positive if the values of R_f for the substances of the analyte mixture and the references are equal. The content of a mixture component can be determined in one of two ways, namely, the coloured zone of a substance is carefully removed from the plate, and next the analyte is eluted from the sorbent by the relevant solvents. The amount of analyte in the eluate is determined by spectrophotometry or photometry. The content of mixture components can also be determined directly from the chromatograms. In this case, two procedures are employed:

(1) The colour intensities of the spots of the analyte mixture of substances are compared visually with similar spots of the reference substances. The areas of the spots are measured with a planimeter or are evaluated from the radii of the zones of the substances by the formula

$$S = \pi R R_1 \quad (2.8)$$

where S is the area of a spot, mm^2 , R and R_1 are the largest and smallest radii of the zones, mm , and $\pi = 3.14$.

(2) The colour intensities of the spots are measured by densitometric or spectrophotometric techniques directly from a chromatogram using densitometers or spectrophotometers of a special design.

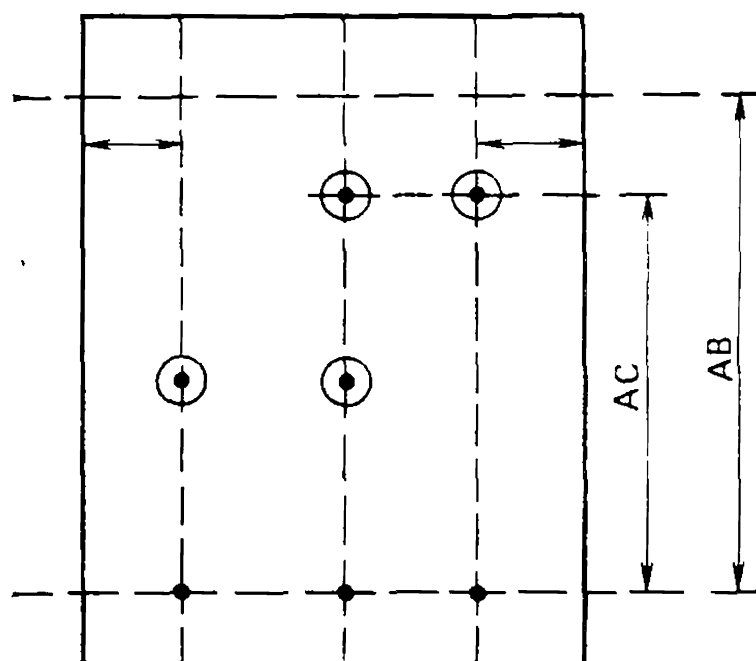


Figure 8. Thin-layer chromatography

ION-EXCHANGE (COLUMN) CHROMATOGRAPHY

Ion-exchange chromatography is based on the exchange of ions between an analyte in a solution and a sorbent.

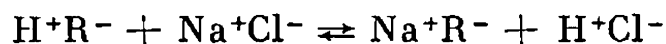
The sorbents contain ionogenic groups and can dissociate and exchange ions with the analyte solution. Such sorbents are known as

ion exchangers. They are high-molecular compounds containing a large number of ionic functional groups and are divided into two types according to the nature of ion exchange, namely, (1) cation exchangers with mobile cations that can be exchanged for the cations from the analyte solution (imparting acidic properties to the ion exchangers), and (2) anion exchangers with mobile anions that can be exchanged for the anions from the analyte solution (imparting basic properties to the ion exchangers).

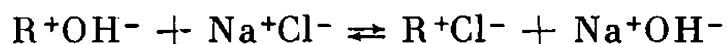
The molecules of cation exchangers of various grades contain mobile SO_3H^- , COOH^- , and other groups. The molecules of anion exchangers contain mobile amino groups, quaternary ammonium bases, etc.

Cation exchangers are available in the hydrogen (H) form and the salt form. The former contain exchange hydrogen ions, and the latter, metal cations. An anion exchanger in the OH form contains exchange hydroxyl ions, and in the salt form, acid anions.

When salts react with cation exchangers in the H form, the process of cation exchange proceeds as follows:



A similar reaction occurs when salts react with anion exchangers in the OH form:



As a result, an equivalent amount of an acid or alkali evolves that can be titrated with the relevant titrant, and then the amount of the analyte salt (NaCl) can be calculated.

Thus, ion-exchange chromatography is not an independent method of quantitative analysis. It is employed as an auxiliary method for separating and extracting substances. The extracted components are then determined by conventional chemical, physical, or physicochemical methods.

Chromatographic separation with ion-exchange sorbents is widely used in quantitative analysis, especially when the quantitative determination of substances without their preliminary separation is impossible. It is employed to determine the concentration of salts in electrolyte solutions, to separate ions by extracting one of them (or a group of ions) from a mixture, and to remove ions interfering with an analysis from a solution.

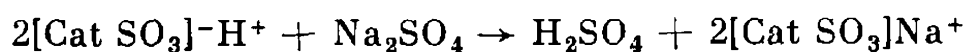
In pharmaceutical analysis, ion-exchange chromatography is widely used for the quantitative determination of salts of organic and mineral acids, salts of alkaloids and nitrogenous bases, and other groups of drugs.

We shall describe two procedures as examples.

1. Quantitative determination of salts of mineral and organic acids. Accurately weigh a specimen of an analyte (0.3-0.5 g), place

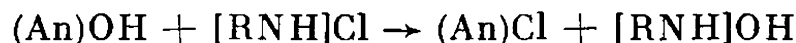
it in a 50-ml volumetric (measuring) flask, and add water up to the mark. Pass 5 ml of the obtained solution through a column with a cation exchanger at a rate of 20 drops a minute. Then rinse the cation exchanger with water (when analysing salts of organic acids, for example sodium benzoate or salicylate, with alcohol) up to a neutral reaction of the effluent, and titrate the evolved equivalent amount of effluent with a 0.1 *N* solution of sodium hydroxide in the presence of the relevant indicator.

Cation exchange follows the reactions:



where Cat is a cation exchanger.

2. Quantitative determination of alkaloid salts and nitrogenous bases. Accurately weigh a specimen of the alkaloid salt being investigated (0.03-0.05 g), dissolve it in 5 ml of water or alcohol, acidify with a drop of dilute hydrochloric acid, and slowly pass the solution through a column containing an anion exchanger. A base of the alkaloid being investigated will separate:



where [RNH] is an alkaloid group, and (An) is an anion exchanger.

Since most alkaloid bases are sparingly soluble in water, for complete elution of such bases, treat the anion exchanger five or six times with 5 ml of 95% alcohol, and then one or two times with 5-10 ml of water until the effluent has a negative reaction to an alkaloid base. To do this, evaporate 3-4 ml of the last filtrate up to two or three drops, and add the relevant reagent for the alkaloid base to the residue. When the base of the alkaloid salt being studied has been eluted completely, determine it in the filtrate by one of the analytical methods.

GAS, GAS-LIQUID, AND LIQUID CHROMATOGRAPHY

Gas and gas-liquid chromatography have come into use in recent years in pharmaceutical analysis. Gas chromatography is especially effective when analysing volatile substances contained in small amounts, for example in complicated natural mixtures of substances.

Gas-liquid chromatography is used in pharmaceutical analysis for the separation, identification, and quantitative determination of drugs and their mixtures. It is especially convenient for control of the quality of substances formed in intermediate synthesis stages. It is also used when studying the stability of various drug forms dur-

ing their storage. Gas-liquid chromatography is quite popular in toxicological investigations and biopharmaceutical analysis because it enables one to determine the concentration of drugs and their decomposition products (metabolites) in a biological material with the required accuracy.

Recently, liquid chromatography (LC) has been introduced at control and analytical laboratories of institutes and industrial pharmaceutical enterprises. The proper choice of two immiscible liquid phases—a mobile and stationary ones—can ensure a high separation at normal temperatures of both volatile and non-volatile substances. Liquid chromatography has already found use in the separation of fatty and amino acids, chelates, alcohols, amines, hydrocarbons, steroids, hormones, alkaloids, antibiotics, and so on.

2.4. BIOLOGICAL METHODS

The chemical or physicochemical methods of analysis cannot be used in pharmaceutical practice for all drugs. Sometimes, a substance has a complicated structure, and it is difficult to find adequate chemical reactions and sufficiently accurate methods of quantitative determinations, moreover because the chemical structure of newly discovered natural substances with a strong biological effect remains undetermined for a certain time. On the other hand, it is not correct to estimate the effect of a drug only using the results of chemical tests because they do not provide exhaustive information on the effect of the drug on an organism. In this connection, it becomes essential to introduce a biological method of analysis characterizing the pharmacological effect of a drug.

Biological tests are conducted on animals and less frequently on separate isolated organs or parts of organs of animals. Generally monkeys, dogs, cats, mice, rats, guinea-pigs, frogs, etc. are the objects of biological investigations.

The effect of drugs in the biological method is expressed in **activity units (AU)** and is determined by comparison with the activity of a reference substance. For example, to establish the biological effect of the insulin hormone, its activity is compared with that of a reference—crystalline insulin containing 24.5 international units per milligramme (the specific activity of 0.04082 mg of this preparation is taken as one unit).

The biological method of investigation is very sensitive. Alkaloids, vitamins, and antibiotics still reveal activity when diluted millions of times.

Notwithstanding a number of its drawbacks, the biological method is still employed quite widely, especially for controlling new medicinal agents whose chemical structure has not yet been established.

REVIEW QUESTIONS

1. What are the tasks of pharmaceutical chemistry?
2. Why do drugs have to meet high purity requirements?
3. What is the essence of the considered methods of analysis (consider each method)?
4. Describe the merits of the modern physicochemical methods of analysis.

PRACTICAL LESSON

Express Analysis of Mixture with Sodium Iodide

1. Carry out an identification reaction. To several drops of the analyte mixture add two or three drops of an iron(III) chloride solution, two drops of acetic acid, and two drops of chloroform, and agitate the mixture. The chloroform layer acquires a violet colour. What is this due to? Give a chemical substantiation of the reaction.

2. Carry out a quantitative determination (the Fajans method). Put 5 ml of the mixture into a 100-ml measuring flask and add distilled water up to the mark. Transfer 5 ml of the diluted solution into a conical (Erlenmeyer) flask, add 5 ml of 2 *N* acetic acid and five drops of a sodium eosinate indicator, and titrate with a 0.1 *N* silver nitrate solution until the precipitate is coloured pink.

3. Calculate the sodium iodide content (*X*) in the solution (in per cent) by formula (1.2), i.e.

$$X = \frac{VKTV_1}{aV_2} \times 100 = \frac{VK \times 0.01499 \times 100}{5.0 \times 5.0} \times 100$$

(here *V* is the volume of the 0.1 *N* silver nitrate solution, ml, and *T* = 0.01499 g/ml).

Analysis of Powders Each Containing 0.005 g of Riboflavin and 0.1 g of Sugar by the Photocolorimetric Method

(a) Using a calibration graph:

1. Dissolve an accurately weighed specimen of riboflavin (0.04 g) in water in a 1000 ml measuring flask with heating. After cooling, add water up to the mark. We shall designate this solution by A. One millilitre of solution A contains 0.00004 g of riboflavin (0.04 mg or 40 µg).

To plot a calibration curve, place an exact amount of solution A into a number of test tubes and dilute with water so that 10 ml of the mixture contains a definite amount of solution A, namely:

Test tube No.	1	2	3	4	5	6	7
Amount of solution A, ml.	1.0	1.5	2.0	2.5	3.0	3.5	4.0
Amount of water added, ml	9.0	8.5	8.0	7.5	7.0	6.5	6.0

2. Calculate the amount of riboflavin in 1 ml of each of the obtained solutions.

3. Determine the maximum absorption of the solutions and choose the required light filter.

4. Determine the absorbance of all the solutions and plot a calibration curve (graph).

5. Using the calibration graph, determine the concentration of riboflavin in an analyte solution.

6. What property of riboflavin is the given procedure based on?
- (b) Using a reference specimen:
1. Dissolve an accurately weighed sample (about 0.01 g) of the preparation in 150 ml of water in a 250-ml measuring flask while heating on a water bath. After cooling, add water up to the mark.
 2. Determine the absorbance of the reference solution. Measure the absorbance of a reference solution containing 2.5 ml of a reference solution of riboflavin and 7.5 ml of water in a cell 10 mm thick using a blue light filter (wavelength 445 nm).
 3. Prepare riboflavin powders. To do this, prepare a mixture for 10 powders by taking 0.05 g of riboflavin and 1.0 g of sugar. Thoroughly triturate the mixture.
 4. Determine the absorbance of the riboflavin in the prepared powders. To do this, dissolve 0.02 g of a powder in 10 ml of water with heating on a water bath. After cooling, add 9 ml of water to 1 ml of the solution. Measure the absorbance in a cell 10 mm thick using a blue light filter.
 5. Determine the riboflavin content in the powders by the formula

$$X = \frac{A \times 0.0001 \times 10 \times b}{A_0 a}$$

where A is the absorbance of the analyte solution, A_0 is the absorbance of a solution of the reference specimen, a is the mass of the specimen, g, and b is the average mass of a powder, g.

Analysis of a 10% Solution of Calcium Chloride by the Refractometric Method

Before performing this assignment, recall the rules of work with a refractometer (see Sec. 2.1).

II. Inorganic Drugs

Chapter 3. Group VIIA Elements

3.1. HALOGEN COMPOUNDS

Group VIIA of the periodic table includes hydrogen and the halogens: fluorine, chlorine, bromine, iodine, and astatine. The first four halogens are encountered in nature. Astatine is prepared artificially and is unstable (radioactive). Fluorine, bromine, and iodine are three of the 15 microelements contained in the human organism. None of the halogens are encountered in nature in the molecular form because their molecules are very reactive.

The halogens are univalent in most of their compounds. This is explained by their electron configuration. The outer electron layer of a halogen atom has seven electrons (two in the *s* and five in the *p* orbitals). Such an atom therefore readily accepts another electron to form a singly charged negative ion with the configuration of the relevant noble gas (ns^2np^6). Hence, the halogens exhibit the properties of non-metals or metalloids and are oxidizing agents. Fluorine attracts an electron the most vigorously, and it is therefore the most electrically negative of all the halogens.

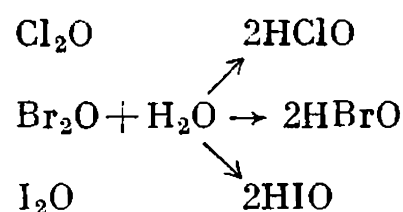
A growth in the atomic mass of the halogens is attended by a decrease in their electronegativity and, consequently, in their oxidizing ability. Thus, fluorine is the strongest oxidizing agent. Next come chlorine and bromine, while iodine is the weakest oxidizing agent of the halogens.

With a view to their oxidizing properties, the halogens are used in medicine chiefly as disinfectants. Fluorine and bromine are very toxic, however, and are not used in medicine. Chlorine is used as an antiseptic for disinfecting water. Iodine is the only halogen used in medicine, in the form of alcohol solutions (5 and 10%).

All the halogens have a very pungent odour. The inhaling of even small amounts of them causes strong irritation of the respiratory tract and inflammation of the mucous membranes. The halogens are most often used in medicine in the form of compounds with other elements. Among them are:

1. Hydrogen halides—the hydrohalic acids (HCl, HBr, HI).
2. Oxygen compounds of the halogens of the general formula Hal_2O , i.e. oxides, which with water yield hypochlorous, hypobro-

mous, and hypoiodous acids, respectively:



The salts of these acids, mainly **hypochlorites** such as NaClO and KClO, as well as chlorinated lime $\text{Ca} \begin{array}{l} \nearrow \text{OCl} \\ \searrow \text{Cl} \end{array}$ are pharmacological preparations.

3. Compounds with alkali metals — **halides** (NaCl, KCl, NaBr, KBr, NaI, KI).

Of the compounds of the first group, only hydrochloric acid is used in medicine. It is the only mineral acid that is constantly present in the free form in the gastric juice of animals and humans. The hydrochloric acid in the gastric juice transforms one of the gastric juice enzymes—pepsin—to the active form. It also destroys the pathogenic and putrefactive bacteria that may penetrate into the stomach. This is why hydrochloric acid is a pharmacological preparation. The State Pharmacopoeia lists two preparations of hydrochloric acid.

Hydrochloric Acid (*Acidum hydrochloricum*)

Dilute Hydrochloric Acid (*Acidum hydrochloricum dilutum*)

HCl

Molecular mass 36.46

Both acids have identical properties and differ only in the amount of hydrogen chloride they contain and, accordingly, in their density.

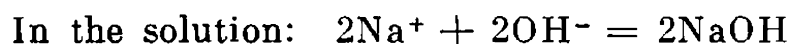
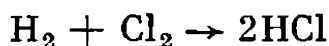
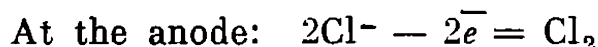
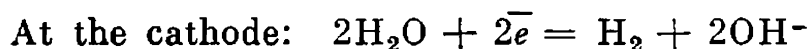
Hydrochloric acid should contain 24.8-25.2% of hydrogen chloride, and its density is 1.125-1.127 g/cm³.

Dilute hydrochloric acid contains 8.2-8.4% of hydrogen chloride, and its density is 1.040-1.041 g/cm³.

Commercial concentrated hydrochloric acid contains 37% of hydrogen chloride, and its density is 1.19 g/cm³. This acid fumes because the hydrogen chloride combines with ammonia, which is always present in the air, to form ammonium chloride, and it is exactly the very minute particles of this compound that form the fume. This is why the acid is called **fuming**.

Hydrochloric acid is prepared by dissolving hydrogen chloride in water. The main method of the industrial production of hydrogen

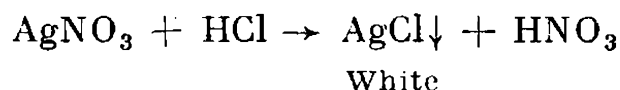
chloride at present is its synthesis from hydrogen and chlorine that are evolved in the electrolysis of a sodium chloride solution:



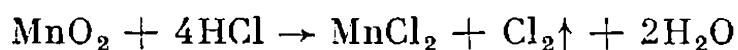
Pharmacopoeial preparations of hydrochloric acid are a colourless transparent liquid, sometimes with a yellowish tint due to an impurity of iron(III) chloride that may get into the preparation from the material of the apparatus used to produce the acid. Hydrochloric acid mixes with water and alcohol in any proportions.

Its presence is confirmed by reactions for the Cl^- anion:

(a) when a silver nitrate solution is added to hydrochloric acid, silver chloride precipitates, which is soluble in an ammonia solution (ammonium hydroxide):



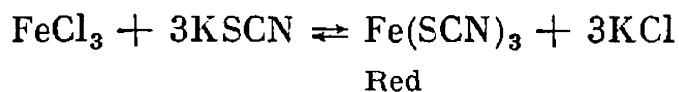
(b) when hydrochloric acid is heated with manganese dioxide, free chlorine evolves (it is the product of oxidation of the Cl^- in the acid to molecular chlorine Cl_2), which is detected by its odour:



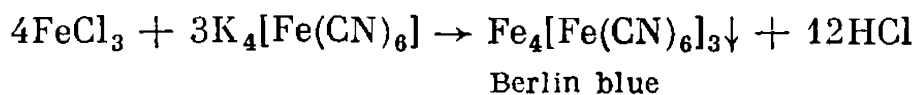
To establish the quality of hydrochloric acid, it is tested for impurities*:

1. Salts of trivalent iron (FeCl_3) are detected by a reaction:

(a) with a potassium thiocyanate solution and the formation of red iron(III) thiocyanate:

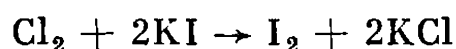


(b) with a potassium ferrocyanide solution and the formation of Berlin blue:



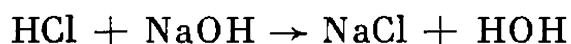
* The sulphate, sulphate ash, and arsenic impurities indicated in the State Pharmacopoeia and due to the previously used sulphate method of producing HCl are of no significance at present because recent years have seen this method going out of use in the industry.

2. Free chlorine is detected by the action of potassium iodide in the presence of chloroform. The iodine displaced by the chlorine colours the chloroform violet:



The concentration of hydrochloric acid can be determined:

(a) by neutralization, i.e. titration with an alkali using methyl orange as an indicator (the method indicated in the State Pharmacopoeia):

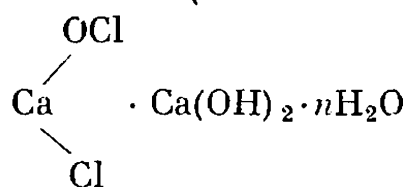


(b) from its density, because a definite value of the density corresponds to a definite acid concentration. Knowing the density, we can easily find the concentration of the acid corresponding to it from tables given in the literature. For example, for a density of 1.19 g/cm³, we find 36.5% of hydrogen chloride, and for 1.125 g/cm³ we find 25% of the hydrogen chloride.

Dilute hydrochloric acid is used in medicine. It is administered orally in drops or in the form of a mixture (most often together with pepsin) to improve gastric acidity. It is often prescribed together with iron preparations because it promotes their absorption.

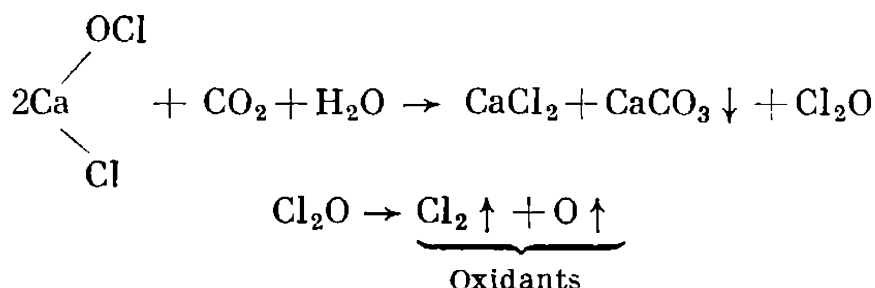
Medicinal hydrochloric acid must be stored at room temperature in bottles with ground glass stoppers. Never store the acid in very warm premises because this may cause a gas (HCl) to evolve that disturbs the sealing of the bottle. The preparation is listed in group B.

Chlorinated Lime (*Calcaria chlorata*)



Among the oxygen halogen compounds, only the salts of hypochlorous acid (hypochlorites) are of interest for medicine, chiefly chlorinated lime—a mixed calcium salt of hypochlorous and hydrochloric acids.

Chlorinated lime is a strong oxidizing agent (oxidant). Under the effect of acids, even such a weak one as the carbonic acid present in the air, it decomposes with the evolution of free active chlorine, and it is exactly the latter that has a disinfecting and deodorizing action:



Chlorinated lime is used as a large-scale degassing agent for the disinfection of premises, cesspools, and refuse pits.

Of the alkali metal halides, sodium and potassium chlorides, bromides, and iodides are pharmacopoeial preparations.

All these drugs have many common features both in the ways they are produced and in their properties and, consequently, the methods of analysing them are similar. But their action on an organisms differs.

Sodium Chloride (*Natrii chloridum*)

NaCl

M.m. 58.44

Potassium Chloride (*Kalii chloridum*)

KCl

M.m. 74.56

The main function of sodium chloride in an organism is to maintain a constant osmotic pressure of the blood. When there is a lack of sodium chloride in an organism, it is introduced intravenously or subcutaneously in the form of a 0.9% aqueous solution known as an **isotonic solution**. Introduction of this solution levels out and normalizes the osmotic pressure of the blood. It is also used for baths, swabbing, and gargling in diseases of the upper respiratory tract.

Sodium chloride is administered in the form of tablets: *Tabulettae Natrii chloridi*, or a 0.9% isotonic solution for injections: *Solutio Natrii chloridi isotonica 0.9% pro injectionibus*.

The other preparation—potassium chloride—is administered in cardiac arrhythmia, especially in intoxication by cardiac glycosides when the myocardium cells become depleted in potassium ions. Potassium chloride is also employed in hypopotassaemia (a decrease in the potassium ion concentration in an organism) caused by the prolonged taking of diuretics.

Potassium chloride is generally prescribed for oral administration in the form of a 10% aqueous solution or in the preparation panangin (potassium magnesium aspartate)*.

Sodium and potassium bromides are used as tranquilizers.

* Since most drugs are known by different names in different countries, the most widely used non-proprietary synonyms (common names) are given in parentheses throughout the book in addition to the names employed in the USSR—*Translator's note*.

Sodium Bromide (*Natrii bromidum*)

NaBr

M.m. 102.90

Potassium Bromide (*Kalii bromidum*)

KBr

M.m. 119.01

The tranquilizing effect of bromine preparations is based on their ability to augment depression in the cerebral cortex. This is why bromides are administered in neurasthenia and increased irritability. Bromides are taken orally in the form of solutions (mixtures) and tablets.

The pharmacopoeial preparations of iodides include:

Sodium Iodide (*Natrii iodidum*)

NaI

M.m. 149.89

Potassium Iodide (*Kalii iodidum*)

KI

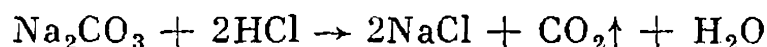
M.m. 166.01

Both preparations are white crystalline powders. Iodides are administered in hyperthyroidosis and endemic goitre.

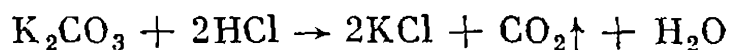
If food or water does not contain a sufficient amount of iodine, which sometimes occurs in certain mountainous localities, the local population acquires a disease called cretinism or goitre. Iodides are prescribed in the form of solutions (mixtures) for oral taking.

Ways of Producing Halides. Sodium chloride is the only halide that occurs widely in nature as massive deposits of rock salt. This is exactly the main source for the production of the pharmacopoeial preparation. Aqueous salt solutions are first evaporated, and then the salt is purified from admixtures. The sodium chloride is finally recrystallized from a saturated aqueous solution of hydrochloric acid in which it dissolves poorly.

A purer preparation can be obtained by treating sodium carbonate with chemically pure hydrochloric acid:



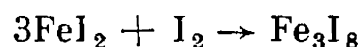
Pure potassium chloride is obtained in the same way, namely:



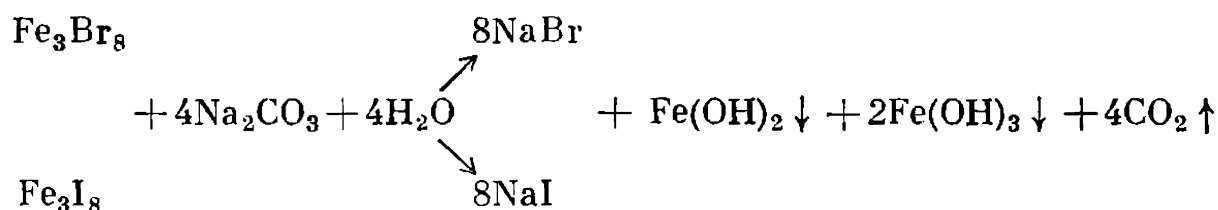
The by-product of the reaction (CO_2) is volatile, and therefore the chlorides produced are pure.

Bromides and iodides are produced in the industry as follows: iron shavings are treated with water and bromine or iodine is added.

The product is iron bromide or iodide (FeBr_2 or FeI_2). Next more bromine or iodine is added to the reaction mixture:



After this, the solution of ferroferric bromide (or iodide) is evaporated and a sodium carbonate (soda) solution is added:

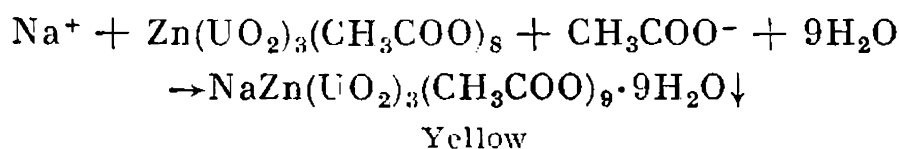


The precipitates of the iron hydroxides are filtered off. After evaporation, sodium bromide (iodide) crystallizes out from the filtrate.

Potash K_2CO_3 is taken instead of soda to produce potassium bromide and potassium iodide.

All these preparations (chlorides, bromides, iodides) are identified by reactions for the cation Na^+ and K^+ and the relevant anion Cl^- , Br^- , and I^- .

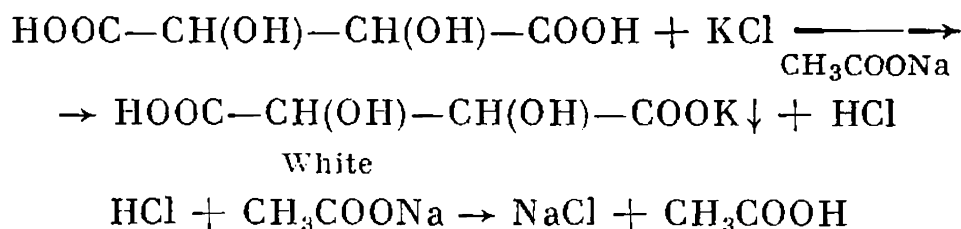
The sodium ion is usually detected by its colouring a flame yellow. The State Pharmacopoeia recommends a reaction with zinc uranyl acetate in dilute acetic acid; yellow crystals precipitate in the presence of Na^+ :



This reaction can be considered as a specific one for the Na^+ ion because most cations do not interfere with it.

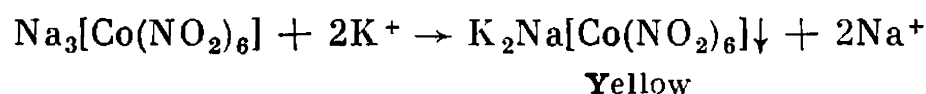
The potassium ion is detected by its colouring a burner flame violet, while if one looks at the flame through a blue glass, it seems to be coloured purple-red. The following chemical reactions are employed:

(a) a reaction with tartaric acid in the presence of sodium acetate:



To prevent the dissolving of the potassium hydrotartrate in the formed mineral acid (HCl), the latter is bound with sodium acetate;

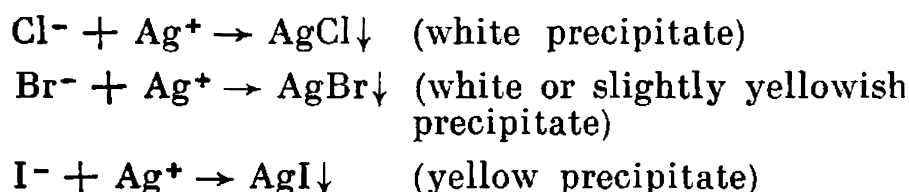
(b) a reaction with a solution of sodium cobaltinitrite:



The reaction is conducted in an acetic acid solution while rubbing a rod against the walls of the test tube. This reaction can be used to detect the potassium ion only in the absence of NH_4^+ ions, which also produce a precipitate with this reagent. Therefore, before testing potassium salts by the given reaction, they must be roasted to remove possible admixtures of ammonium salts.

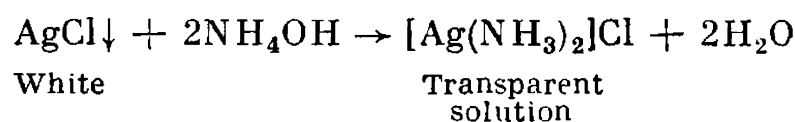
Two main reactions are recommended for identifying the anions Cl^- , Br^- , and I^- , namely,

(a) a reaction with a silver nitrate solution in the presence of nitric acid:



The nitric acid does not dissolve the silver halide precipitates.

Since silver chlorides and bromides are sometimes difficult to distinguish by their colour, it is recommended to test the solubility of these precipitates in solutions of ammonia and ammonium carbonate $(\text{NH}_4)_2\text{CO}_3$. Silver chloride readily dissolves in dilute solutions of these substances with the formation of the relevant soluble complexes:



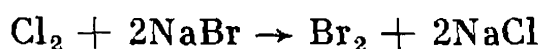
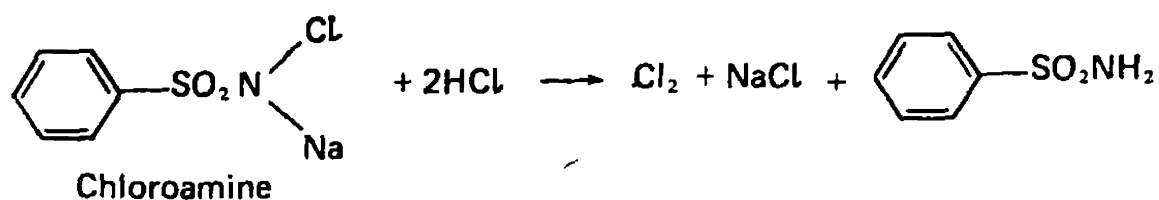
Silver bromide dissolves sparingly in dilute ammonia solutions, but does dissolve only in concentrated solutions, while it does not dissolve at all in an ammonium carbonate solution.

Silver iodide dissolves neither in an ammonia nor ammonium carbonate solutions:

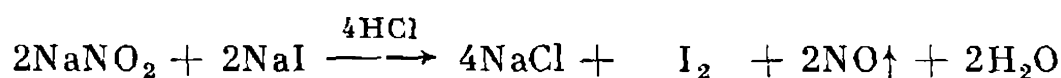
(b) a reaction of oxidation of the halide ions (Cl^- , Br^- , I^-) to the elementary halogen. Halide ions are reducing agents in an acidic medium and can be oxidized to the free halogen. This property is used to identify bromides and iodides.

A mineral acid, for example, hydrochloric acid, chloroform, and an oxidizing agent are added to a bromide or iodide solution (NaBr, NaI). Generally chloroamine is added as the oxidant when dealing with bromides, and sodium nitrite NaNO_2 or iron(III) chloride FeCl_3 when dealing with iodides. The reaction mixture is agitated

and left to settle. The chloroform layer becomes coloured yellow (Br_2) or violet (I_2), respectively:



Yellow in
chloroform

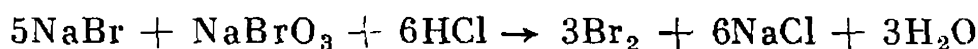


Violet in
chloroform

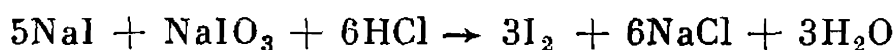
(Identical reactions occur with KBr and KI).

Chlorides (NaCl , KCl) are also oxidized to free chlorine, but since chlorine is volatile, this reaction is not convenient for identifying chlorides and is not recommended by the State Pharmacopoeia.

Bromates (NaBrO_3) and iodates (NaIO_3) are often employed for detecting bromides and iodides. They are oxidizing agents and in an acidic medium oxidize Br^- and I^- to free bromine and iodine. The reaction is conducted in the presence of chloroform, which is coloured yellow (Br_2) or violet (I_2):



Yellow



Violet

Purity Test. The State Pharmacopoeia requires that sodium and potassium chlorides contain no admixtures of magnesium, barium, and ammonium salts. Sodium chloride must not contain any admixtures of potassium salts, and vice versa, because potassium and sodium are antagonists in their effect.

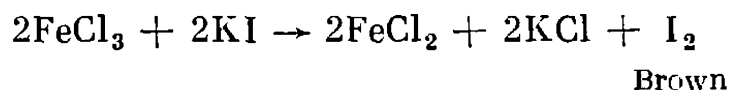
Impurities such as calcium, iron, heavy metals, sulphates, and arsenic are permitted by the State Pharmacopoeia in sodium and potassium chloride preparations within the limits of standard specimens because the tolerated limit of these impurities does not affect the therapeutic action of the preparations and does not cause any side effects.

Bromides must contain no admixtures of barium, calcium, bromates, and iodides (toxic).

An admixture of soluble barium and calcium salts is determined by adding dilute sulphuric acid to a solution of the analyte preparation. When Ba^{2+} or Ca^{2+} (or both) are present, turbidity of the so-

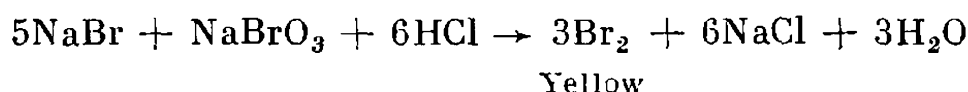
lution will be observed owing to the formation of insoluble calcium and barium sulphates (CaSO_4 and BaSO_4).

An admixture of iodides is determined by adding an oxidizing agent such as iron(III) chloride to the preparation solution:



When chloroform is added, the evolved iodine colours it violet.

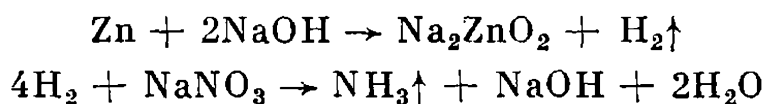
Bromates are the most dangerous impurity owing to their toxicity. They can be detected in bromides by adding hydrochloric acid. When bromates are present, free bromine will evolve, which colours the solution yellow:



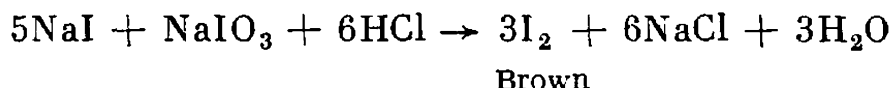
Admixtures of sulphates, heavy metals, and arsenic are tolerated in bromides within the limits of the standards.

Iodides can contain admixtures of carbonates, cyanides, nitrates, iodates, and soluble barium salts. All these admixtures are poisonous, and therefore they are not tolerated in preparations.

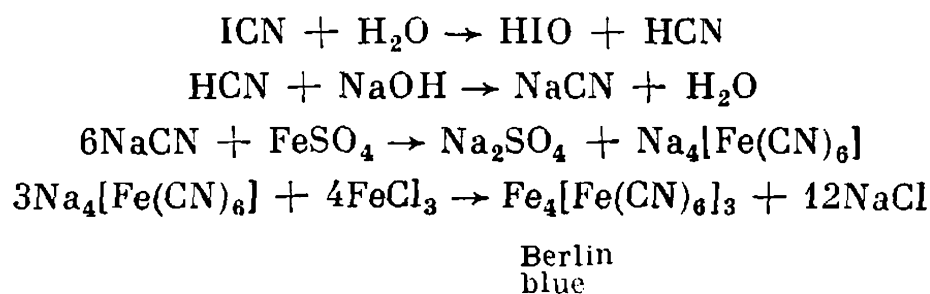
An admixture of nitrates is detected by reducing them to ammonia, which is determined organoleptically or by wet red litmus paper turning blue:



An admixture of iodates (NaIO_3) is determined like one of bromates:



An admixture of cyanides is determined by the formation of Berlin blue:



The State Pharmacopoeia recommends the *quantitative* determination of chlorides and bromides by argentometry (by the Mohr method). An exactly weighed specimen of the analyte preparation is titrated in a neutral or weakly alkaline medium with a silver nitrate solution

Seaweeds, the residues in the production of saltpetre, and oil-field waters can be sources for the commercial production of iodine. The first two sources were used for this purpose up to the World War I, but since they have a low iodine content, they could not satisfy the demand for this preparation. This explains the acute shortage of iodine in many countries at that time.

The problem of producing iodine in the USSR was solved by O. Magidson and his collaborators. They proposed to use oil-field waters as a source for producing iodine.

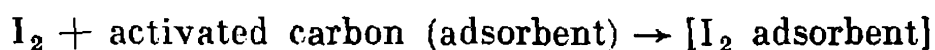
Iodine-bearing oil-field waters were known long ago, but not a single country in the world used this very rich source. The waters themselves contain a small amount of iodine (20-40 mg per litre), but their supplies are so large that this source has no equal as regards its profitability.

Since the concentration of iodine in oil-field waters is very low, it was necessary to find a way of increasing its extraction from the waters. This can be done in two ways, namely, by adsorbing the iodine with an appropriate adsorbent or by extracting it with an organic solvent. Magidson chose the adsorption method. Initially starch was used as the adsorbent, but this increased the cost of iodine production, therefore activated carbon was later proposed as the adsorbent.

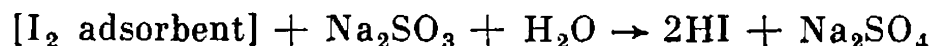
The process of extracting iodine from oil-field waters can be illustrated schematically as follows. The iodides in the waters are oxidized to convert the ionogenic iodine to the molecular form:



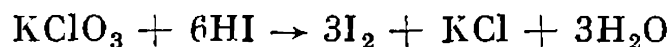
The evolved free iodine is adsorbed by activated carbon:



The iodine is extracted from the adsorbent by the action of reducing agents such as sodium sulphite that converts the I_2 back to I^- :



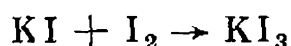
The concentration of I^- in the obtained solution at the given stage is already from 200 to 300 times greater than that in the oil-field waters. The iodide is further oxidized to the molecular form by the action of oxidizing agents:



At present, the demand for medical iodine is completely satisfied in the USSR, and it is even exported to a number of foreign countries. The pharmacopoeial preparations of iodine are crystalline iodine and a 5% and 10% alcohol solution.

Iodine is a grayish black substance occurring in scales with a metallic lustre or crystal intergrowths with a pungent odour. Iodine

is volatile even at ordinary temperatures. When heated, it sublimes and forms a violet vapour. It dissolves sparingly in water, and better in alcohol and glycerin. It readily dissolves in a potassium iodide solution to form potassium periodide:



Iodine is coloured differently in different solvents, namely, in chloroform and carbon disulphide it is violet, in alcohol and ether it is brown.

As regards its chemical properties, iodine is a weaker oxidizing agent than the other halogens. The reaction of iodine with a starch solution is a specific reaction for it: in the presence of iodine, the starch becomes coloured blue.

The quality of iodine is determined by the absence of mineral impurities and mechanical ones (graphite). Depending on how the iodine was produced, the mineral impurities can include iodine cyanides when the source was seaweeds, and chlorine, if Cl_2 was used as an oxidizing agent in the iodine production process. The impurities are determined by the relevant analytical reactions.

For the quantitative determination of iodine, its accurately weighed specimen is dissolved in a potassium iodide solution and is titrated with sodium thiosulphate (starch is the indicator).

Iodine has an antimicrobial effect, therefore its solutions are employed for treating wounds.

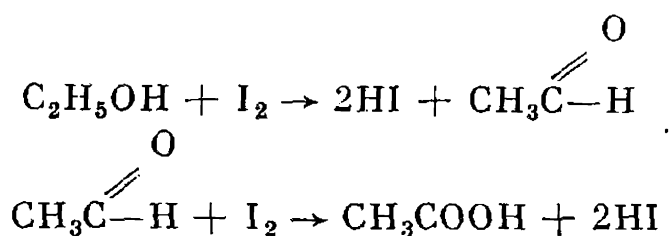
In accordance with its chemical properties, iodine is stored in bottles with ground glass stoppers (iodine erodes cork stoppers) in a cool place protected from light. It belongs to group B drugs.

5% and 10% Alcohol Solution of Iodine (*Solutio jodi spirituosa 5% aut 10%*)

A 10% alcohol solution of iodine is prepared by dissolving it in 95% alcohol.

A 5% alcohol solution of iodine is prepared using dilute alcohol with the addition of potassium iodide (2%).

A 10% iodine solution prepared with pure 95% alcohol is not stable and after some time (6-8 weeks) the iodine content in it diminishes. The explanation is that the alcohol is oxidized by the iodine to an aldehyde, and the latter is further oxidized by the iodine to an acid. The solution thus has an acidic reaction:



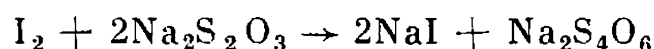
With a view to the possible oxidizing processes in an iodine solution during prolonged storage, a 10% alcohol solution of iodine should be prepared for a short period (up to one month).

When the iodine in this solution is being determined quantitatively, the State Pharmacopoeia requires that the amount of hydroiodic acid HI possibly present in this preparation also be determined. For this purpose, the iodine is first titrated with sodium thiosulphate in the iodine solution taken for analysis, and then in the decolorized solution the HI is titrated with an alkali using phenolphthalein as an indicator.

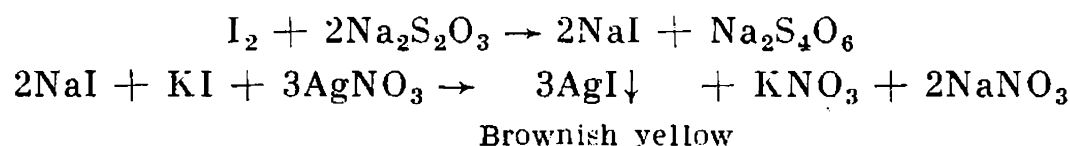
A 5% alcohol solution of iodine is a stable preparation, which is explained by the stabilizing effect of the KI present in this solution.

Iodine is identified in 5% and 10% alcohol solutions by the same reactions used for crystalline iodine.

For the quantitative determination of iodine in a 5% alcohol solution, it is titrated with sodium thiosulphate:



The State Pharmacopoeia simultaneously requires the determination of the potassium iodide contained in the solution. After titration of the iodine with sodium thiosulphate, the solution loses its colour, sodium eosinate (an indicator) and acetic acid are added to it, and it is titrated with a silver nitrate solution until the liquid becomes pink. Here the potassium iodide in the iodine solution is titrated, as well as the sodium iodide formed in the titration of the iodine with sodium thiosulphate:



The amount of KI in the preparation is determined from the difference between the second and first titrations. The State Pharmacopoeia requires a KI content in the preparation of at least 1.9% and at most 2.1%.

The 5% and 10% alcohol solutions of iodine are employed as antiseptic and irritant (counter-irritant) agents in inflammatory diseases of the skin and mucous membranes. These alcohol solutions of iodine are also taken orally in the form of drops for the prophylaxis of arteriosclerosis.

A solution of iodine and potassium iodide in water, called Lugol's solution (*Solutio Lugoli*) is employed in medicine for smearing the mucous membranes of the larynx and pharynx. Alcohol solutions of iodine are stored in orange glass bottles (because light accelerates the oxidation processes) with ground glass stoppers.

REVIEW QUESTIONS

1. Explain why the halogens are generally not encountered in nature in the free form.
2. What chemical properties do the halogens have?
3. Describe the physical properties of chlorine, fluorine, bromine, and iodine.
4. Which of the enumerated elements is a stronger oxidizing agent and why?
5. What role do potassium and sodium ions play in a human organism?
6. Can sodium chloride be replaced with potassium chloride? Explain your answer in detail.
7. Why should 10% alcohol solutions of iodine be stored not longer than one month? Give a chemical explanation.
8. Why should the Mohr method not be used for the quantitative determination of iodides?
9. Why does sodium iodide turn yellow in the air?
10. Why are iodides and bromides stored in dark glass bottles in a dark place?

PRACTICAL LESSON

Analysis of a 10% Potassium Iodide Solution

1. Conduct an identification reaction.
To 1-2 ml of the analyte mixture add 2-3 drops of an iron(III) chloride solution, 2 drops of acetic acid, and 2 drops of chloroform. Agitate the solution: the chloroform layer turns violet. Write the equation of the chemical reaction.
2. Carry out a quantitative determination (the Fajans method).
Put 5 ml of the mixture into a 100-ml measuring flask, add water up to the mark, and mix the solution. Transfer 5 ml of the latter into an Erlenmeyer flask, add 5 ml of 2 *N* acetic acid and 5 drops of a sodium eosinate indicator, and titrate with a 0.1 *N* silver nitrate solution until the precipitate becomes pink. Write the equation of the chemical reaction.
3. Calculate the potassium iodide content in per cent in the solution by formula (1.2):

$$X = \frac{VKTV_1}{aV_2} \times 100 = \frac{VK \times 0.0166 \times 100}{5.0 \times 5.0} \times 100$$

Here *V* is the volume of a 0.1 *N* silver nitrate solution, ml, *T* = 0.0166 g/ml, and *a* is the volume of the preparation taken for the determination, ml.

4. Arrive at a conclusion on the potassium iodide content in the solution (in per cent).
5. What other method can be used to determine potassium iodide quantitatively?

Analysis of a 3% Sodium Bromide Solution

1. Write the prescription in Latin.
2. Conduct an identification reaction.
To 1 ml of the mixture add 1 ml of dilute hydrochloric acid, 0.5 ml of a chloroamine solution, 1 ml of chloroform, and agitate the solution. The chloroform layer acquires a yellow-brown colour. Write the equation of the chemical reaction.
3. Carry out a quantitative determination (argentometry, the Mohr method).

Put 5 ml of the mixture into a 100-ml measuring flask, add water up to the mark, and thoroughly mix. Transfer 5 ml of the diluted solution into an Erlenmeyer flask, add 2-3 drops of potassium chromate, and titrate with a 0.1 *N* silver nitrate solution up to the formation of a brick red precipitate. Write the equations of the chemical reactions.

4. Calculate the content of sodium bromide in the solution in per cent by formula (1.2):

$$X = \frac{VKTV_1}{aV_2} \times 100 = \frac{VK \times 0.01029 \times 100}{5.0 \times 5.0} \times 100$$

where *V* is the volume of the 0.1 *N* silver nitrate solution, ml, and *T* = 0.01029 g/ml.

5. Conclude whether the solution actually contains bromides, find their content, and establish whether the solution may be dispensed.

Analysis of Sodium Chloride

Control the quality of sodium chloride with respect to all its characteristics according to the official requirements.

Chapter 4. Group VIA Elements

Of the Group VIA elements, oxygen and sulphur are of interest for medicine. They themselves are pharmaceutical preparations, and some of their compounds are also of importance.

The chemical properties of group VIA elements point to the sharply expressed non-metallic nature of these elements. This is due to the outer electron layers of their atoms accommodating six electrons—two in the *s* orbital and four in the *p* orbital. The covalence of oxygen is generally two. But an oxygen atom having unshared electron pairs can sometimes be an electron donor and form additional covalent bonds.

The group VIA elements exhibit both a negative and positive oxidation state in their compounds. In compounds with metals and hydrogen, their oxidation number is generally -2 . In compounds with non-metals, it can be $+4$ and $+6$. Oxygen itself is an exception. In compounds with fluorine, its oxidation number is $+2$, while in compounds with all the other elements it is negative and equals -2 .

4.1. OXYGEN COMPOUNDS

Oxygen (*Oxygenium*)

O₂

M.m. 32.00

Oxygen is a pharmaceutical preparation and is described in the State Pharmacopoeia. It is employed for inhalation in various kinds of hypoxaemia (insufficient oxygenation of the blood).

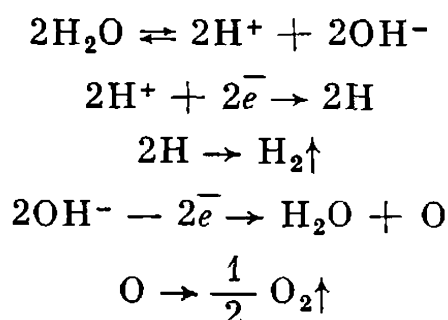
Oxygen is the most widespread element in the Earth's crust. In the free state it is contained in the atmosphere (23%), in the bound state it is present in water, minerals, rock, and in all substances from which the organisms of plants and animals are built up.

Oxygen was first obtained in the pure form by K. Scheele (1772). J. Priestley (England) described the most important properties of oxygen—its ability to support combustion, and its role in breathing. The French chemist A. Lavoisier, who studied the properties of oxygen in detail, established that it is a constituent part of the air.

Oxygen is produced commercially from the air. At a temperature of -140°C and a pressure of about 4 MPa, air condenses into a colourless transparent liquid; the latter is exactly what is used to produce oxygen, nitrogen, and the noble gases. They are separated by fractional distillation.

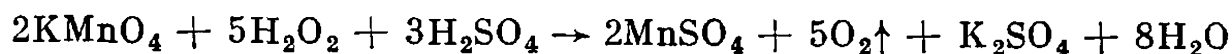
The main laboratory method of producing oxygen is the electrolysis of aqueous solutions of alkalis or acids. Here the hydrogen ions migrate toward the cathode, where they gain an electron and transform into neutral atoms forming hydrogen molecules. The latter are evolved at the cathode.

The hydroxide ions become discharged at the anode with the formation of water and oxygen:

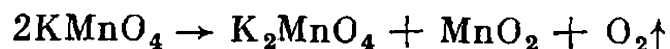


Small amounts of oxygen can be produced under laboratory conditions by:

(1) reacting potassium permanganate with a hydrogen peroxide solution in the presence of an acid:



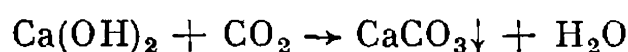
(2) the thermal decomposition of potassium permanganate:



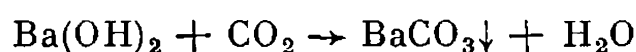
Oxygen is a colourless gas without an odour and taste. It supports combustion. This property of oxygen is used to identify it, namely, a glowing splinter introduced into a vessel filled with oxygen ignites and burns with a bright flame.

The oxygen intended for medical administration must be free of any possible impurities. The oxygen obtained from air may contain admixtures of CO_2 , NO , NO_2 , and CO .

Carbon dioxide CO_2 forms in nature in the combustion of wood and coal, breathing, and in decay. Especially large amounts of CO_2 , as well as carbon monoxide CO , are discharged into the atmosphere in large industrial centres. The presence of CO_2 in oxygen is detected by passing the oxygen through baryta or lime water. Turbidity of the solution due to the formation of barium or calcium carbonates points to the presence of a CO_2 impurity:

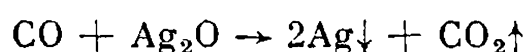


White



White

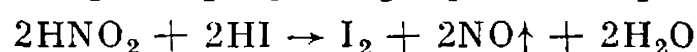
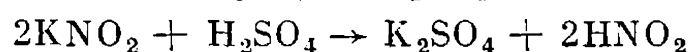
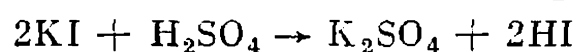
Admixtures of CO are detected by taking advantage of its reducing properties. The oxygen is passed through an ammonia solution of silver nitrate AgNO_3 . If a CO admixture is present, the solution becomes dark or a precipitate of free silver forms:



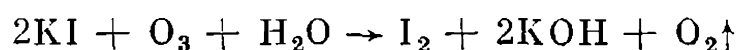
Black

Nitrogen oxides (NO_2 , NO) may appear in the air when electrical discharges occur in the atmosphere.

Nitrogen oxides are detected by passing the oxygen through an alkali with the subsequent addition of acidified potassium iodide. If nitrogen oxides are present, the solution turns yellow owing to the evolution of iodine. When starch is added, the liquid becomes blue:



An admixture of oxidizing substances such as ozone can be detected by passing the oxygen through a potassium iodide solution to which starch has been added. If ozone is present, a blue colour appears owing to the evolution of iodine:



The quantitative determination of oxygen is performed with the aid of an absorbing solution containing a copper-ammonia complex. A Hempel apparatus is used for this purpose.

Oxygen is delivered to pharmacies in blue steel cylinders under a pressure of 120-150 atm. The cylinders must be kept in cold basements. The cocks and threading of the cylinders must never be lubricated with grease because the released oxygen can ignite organic substances. The cocks are generally coated with talc. At the pharmacies, oxygen is dispensed in rubber bags provided with a long rubber tube

having a cock. When bags are being filled with oxygen from a cylinder, the oxygen should be passed through wash bottles with water.

Pure oxygen is used in medicine for inhalation in various types of hypoxaemia of the tissues, for example in poisoning by carbon dioxide or chlorine, in insufficient supply of atmospheric oxygen to the blood because of inflammatory processes or other diseases of the respiratory organs, in asphyxia, etc. Oxygen is administered to a patient via a mouthpiece (wrapped in moist gauze) connected by a rubber tube to an oxygen bag.

The compounds of hydrogen with oxygen—distilled water and hydrogen peroxide—are pharmacopoeial preparations.

Distilled Water (*Aqua destillata*)

H₂O

M.m. 18.02

Ordinary potable water contains many organic and inorganic impurities. The latter may include sulphates, nitrates, chlorides, calcium and magnesium oxides, and small amounts of ammonia.

Natural water is thus a solution containing a multitude of various salts. Such water cannot be used in pharmacy practice for preparing medicinal agents because the salts contained in it may harm many pharmaceutical preparations, while organic impurities create favourable conditions for the development of pathogenic microorganisms. This is why water purified from organic and inorganic impurities by distillation is used in pharmacology. Such water is called **distilled**.

But distilled water almost always contains insignificant amounts of foreign substances that get into it either from the dust of the air or owing to the leaching out of the glass in which it is stored, or in the form of traces of the metal from which the refrigerator tubing is made. Moreover, gases (NH₃, CO₂) dissolved in the water and some volatile organic compounds present in it may pass together with the water vapour into the receiver during distillation. Finally, salts may get into the distillate as a result of the entrainment of very minute water droplets by the vapour.

Distilled water must be colourless, transparent, without an odour and taste. Its pH must be within 5.0-6.8, its specific gravity at 4 °C must equal 1.000, and its boiling point at a pressure of 760 mm Hg must be 100 °C. These properties determine the authenticity and at the same time the proper quality of distilled water. A number of tests are recommended for controlling the quality of distilled water. They determine the absence or tolerated limit of various impurities.

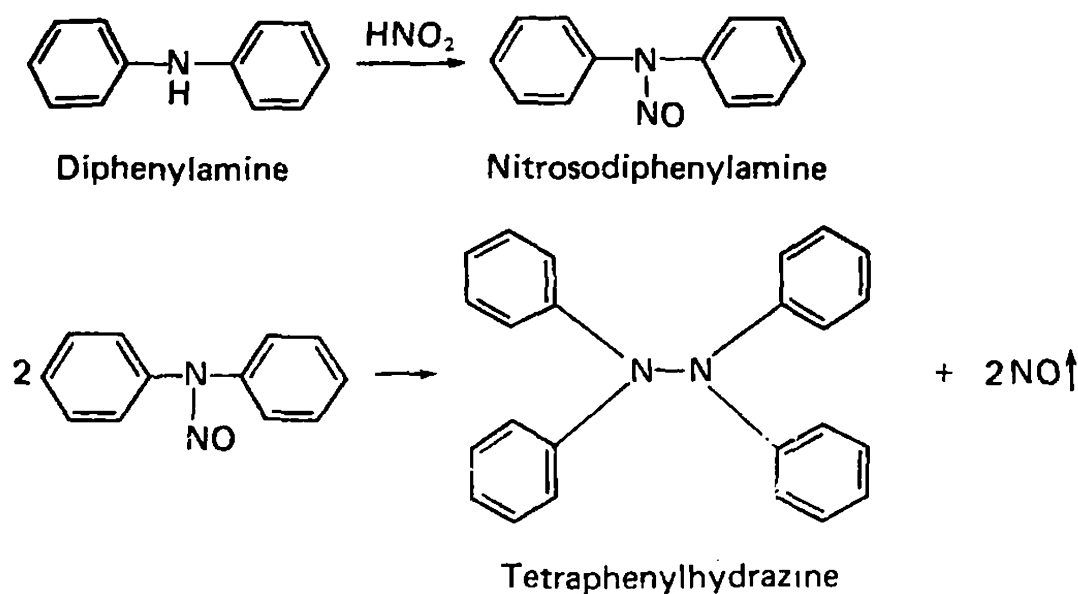
First of all the reaction of water is tested. To do this, several drops of methyl red are added to a small amount of freshly distilled water: pure water is neutral, and therefore its colour should become yellow when the indicator is added. The further addition of a drop of a

0.01 *N* hydrochloric acid solution should cause a pink colour to appear.

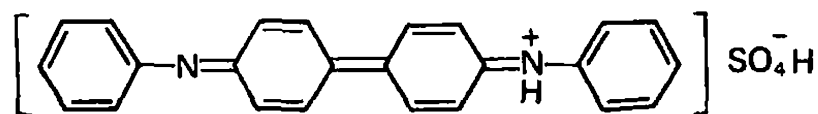
To test for salt admixtures, a small amount of the water is evaporated. Pure water should leave no dry residue after its evaporation. A dry residue not exceeding 1 mg (0.001%) is tolerated by the State Pharmacopoeia after the evaporation of 100 ml of distilled water.

Distilled water must have no positive reactions to chlorides, sulphates, and salts of calcium and the heavy metals. The presence of a carbon dioxide impurity is also not tolerated. If the latter is present, it can be detected by the turbidity of lime or baryta water taken in an equal volume with the water. This reaction must be conducted in a closed vessel excluding any possibility of carbon dioxide getting into it from the air.

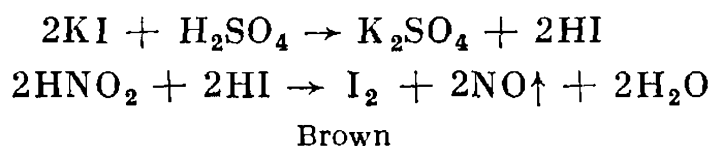
Possible admixtures of nitrates and nitrites are detected by the reaction with a solution of diphenylamine in sulphuric acid (a blue colour). For example:



A salt of diphenyldiphenylquinonediimine causing the blue colour of the solution forms in the long run in the sulphuric acid medium:



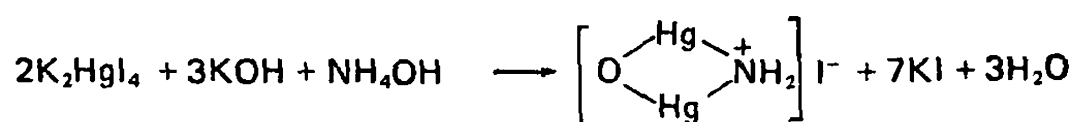
Nitrous acid or its salt can also be detected using a reaction with potassium iodide in the presence of sulphuric acid:



Distilled water intended for injections (*Aqua destillata pro injectionibus*), in addition to the tests indicated above, must be tested for a pyrogen, i.e. various microorganisms.

Organic (reducing) impurities in water set up conditions for the development in it of various mould fungi, bacteria, saprophytes, etc. Hence, a test for organic impurities is obligatory for distilled water. For this purpose, to 100 ml of the water being tested there is added 1 ml of a 0.01 *N* solution of potassium permanganate acidified with dilute sulphuric acid, and the water is heated up to its boiling point. If the pink colour of the water remains unchanged, reducing substances are absent. Should the water contain organic impurities, the potassium permanganate solution loses its colour.

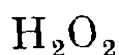
Water may sometimes be contaminated with ammonia and ammonium salts. It is recommended to test it for the presence of these impurities. Ammonia is usually detected by the Nessler reagent producing a yellow or brown colour of the precipitate or liquid:



Distilled water may contain not over 0.000 02% of ammonia.

It should always be stored in well sealed large bottles filled up to their top. The stoppers closing the bottles should be provided with a calcium chloride tube filled with soda lime and cotton wool to prevent carbon dioxide from getting into the water. Prolonged storage in glass vessels even made from chemically stable glass always results in contamination by leaching products. Consequently, distilled water cannot be stored for a long time. The State Pharmacopoeia allows it to be stored at most three days.

Hydrogen Peroxide (*Hydrogenium peroxydi*)

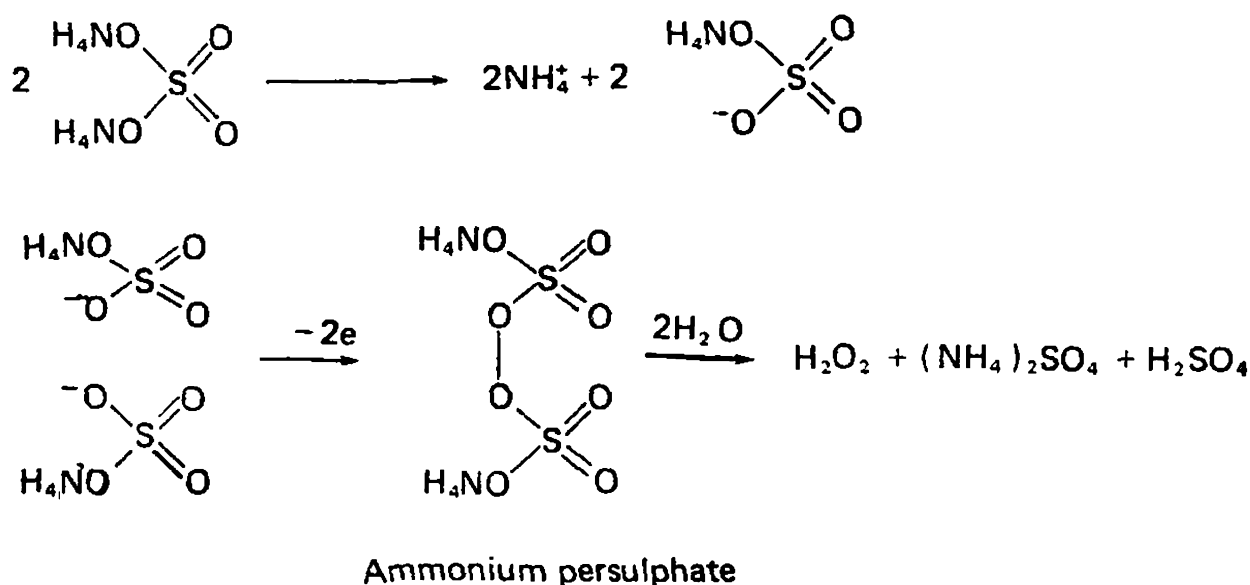


M.m. 34.01

Hydrogen peroxide was discovered by L-J. Thenard (1918) when performing laboratory tests.

Hydrogen peroxide forms in nature as a result of various oxidation processes. It is produced commercially by the electrolysis of acid ammonium sulphate solutions. Here the ammonium ion NH_4^+ discharges at the cathode and forms NH_3 , while at the anode two ammonium sulphate residues give up two electrons and form ammonium persulphate. The latter is decomposed by water with the for-

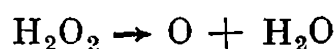
mation of hydrogen peroxide:



Weak hydrogen peroxide solutions are generally obtained in this way. They are concentrated by vacuum distillation at room temperature.

A hydrogen peroxide solution (*Solutio Hydrogenii peroxydi diluta*) containing 2.7-3.3% of H_2O_2 is the pharmacopoeial preparation. It is prepared from more concentrated solutions containing 27.5-31.0% of H_2O_2 and called **perhydrol** (*Perhydrolum*) and is a colourless transparent liquid having a weakly acidic reaction. It has a smarting astringent taste and mixes with water in any proportions.

The structural formula of hydrogen peroxide $\text{H}-\text{O}-\text{O}-\text{H}$ reveals that two oxygen atoms are bound to each other. This bond is not stable, which underlies the instability of the molecule. Hydrogen peroxide decomposes with the evolution of oxygen:

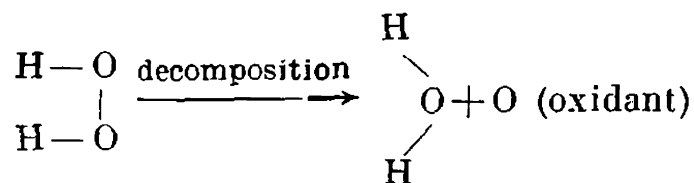


Light, heating, an alkaline medium, and oxidizing or reducing agents accelerate the decomposition of hydrogen peroxide. The salts of some heavy metals (Cu, Mn, etc.) are especially active catalysts of the decomposition of hydrogen peroxide.

To prevent or inhibit this decomposition, various stabilizers (sodium pyrophosphate $\text{Na}_2\text{P}_4\text{O}_{10}$, uric, oxalic, salicylic acids, barbitol, antifebrin, etc.) are added to a hydrogen peroxide solution. The pharmacopoeial preparation of hydrogen peroxide contains antifebrin (acetanilide) as the stabilizer.

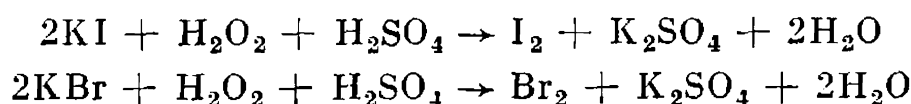
The main chemical property of hydrogen peroxide is its ability to exhibit both oxidizing and reducing properties. The oxidizing properties are much stronger than the reducing ones because H_2O_2 rea-

dily decomposes with the evolution of oxygen:

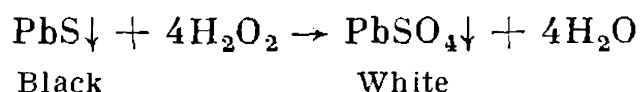


This decomposition is favoured more by an acidic medium.

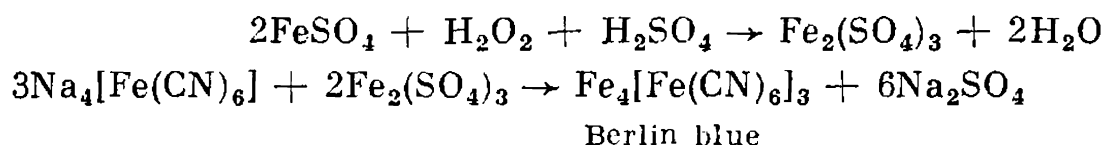
Examples of reactions where hydrogen peroxide exhibits oxidizing properties are its reactions with iodides and bromides:



There are other reactions characterizing the oxidizing properties of hydrogen peroxide, namely, black lead sulphide PbS when reacted with hydrogen peroxide transforms into white lead sulphate:



Hydrogen peroxide oxidizes iron(II) compounds to iron(III) ones. The latter can be detected by the formation of Berlin blue:

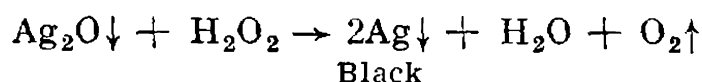


All these reactions can be used to confirm the identity of the preparation.

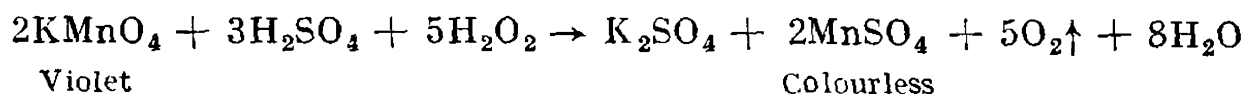
Hydrogen peroxide oxidizes many organic substances (hair, textile fibres, etc.). Its dilute solutions are used as a decolorizing and bleaching agent, and in medicine as a disinfectant.

In some reactions, hydrogen peroxide exhibits reducing properties. For example:

(1) when hydrogen peroxide is reacted with silver oxide precipitated by ammonia from a silver nitrate solution, a black precipitate of reduced silver is observed:

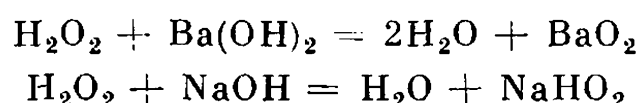


(2) when hydrogen peroxide is reacted with an acidified solution of potassium permanganate, the solution becomes colourless owing to the reduction of the MnO_4^- to Mn^{2+} ; this is attended by the vigorous evolution of oxygen:

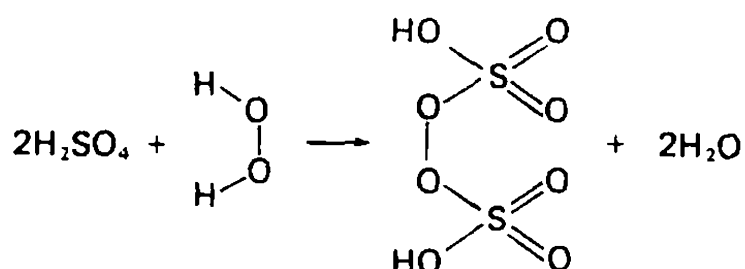


These reactions can also be used to confirm the identity of hydrogen peroxide.

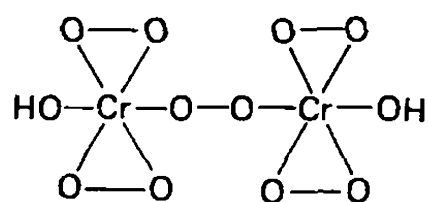
Hydrogen peroxide has weak acidic properties. Its acidic nature is confirmed by the fact that when it is reacted with the hydroxides of some metals, the relevant peroxides form, which can be considered as the salts of hydrogen peroxide:



Hydrogen peroxide is also featured by its ability to form peracids exhibiting strong oxidizing properties:



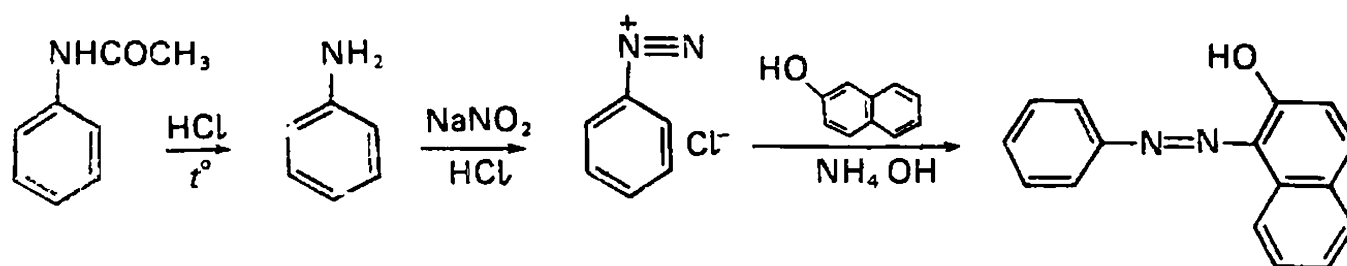
The identity of hydrogen peroxide is often confirmed in analysis by the formation of perchromic acids. The latter depending on the conditions under which the reaction is conducted vary in composition and have different colours but mainly blue. The State Pharmacopoeia recommends a reaction with potassium dichromate in an acidic medium for this purpose. Depending on the conditions of the reaction (temperature, H_2O_2 concentration, etc.), perchromic acids of a various composition can be obtained. For example, when a 30% solution of H_2O_2 is reacted with potassium dichromate cooled to 0°C , blue perchromic acid $\text{H}_2\text{Cr}_2\text{O}_{12}$ is obtained:



When a hydrogen peroxide solution is reacted with a dilute solution of potassium dichromate (at room temperature) acidified with dilute sulphuric acid, the product is perchromic acid HCrO_5 also coloured blue.

Since the peroxide compounds of chromium are not stable in an aqueous solution and rapidly decompose, ether, in which these compounds are more stable, is added to the reaction mixture. After agitation, the ether layer acquires the relevant colour (blue, red, or dark violet depending on the composition of the perchromic acid or perchromate). When the solution is left standing, the blue colour turns green owing to the transition of the hexavalent chromium to trivalent chromium sulphate.

The State Pharmacopoeia also requires the identification of the antifebrin (acetanilide) included in the hydrogen peroxide solution as a stabilizer. For this purpose, a definite amount of the analyte solution of hydrogen peroxide is evaporated, hydrochloric acid is added to the dry residue (antifebrin) and boiled, and then a reaction for a primary aromatic amine (a reaction of an azodye formation) is conducted:



A hydrogen peroxide preparation may have an excess acidity due either to the way of preparing it or to the addition of acids (oxalic, phosphoric, etc.) as stabilizers. This is why the State Pharmacopoeia establishes an acidity limit, which is determined by the titration of a definite volume of the preparation solution with an alkali solution.

The most popular of the volumetric methods of determination are the iodimetric and permanganatometric ones based on the oxidizing and reducing properties of hydrogen peroxide. Permanganatometry is one of the most accurate and reliable techniques for its quantitative determination and can be employed both for dilute and for more concentrated solutions (the method has been adopted by the State Pharmacopoeia).

Analysis is performed by the direct titration of an acidified solution of hydrogen peroxide with a solution of potassium permanganate until the titration end point is reached, i.e. when the solution acquires a pale pink colour.

The iodimetric method of determining hydrogen peroxide is based on its reaction with potassium iodide in an acidic medium. The evolved iodine is titrated with sodium thiosulphate. This method is somewhat less accurate than the permanganatometric one, but it is nevertheless used quite widely, especially for hydrogen peroxide concentrations ranging from 1 to 6%.

New methods of quantitative determination of hydrogen peroxide have been developed during recent years. In addition to the classical volumetric methods of analysis based on the oxidizing and reducing properties of hydrogen peroxide, physicochemical methods of its determination have appeared (gasometric, colorimetric, ultraviolet spectrophotometric, refractometric).

Among the physical methods of determining the concentration of hydrogen peroxide solutions, the method of refractometry deserves mention. After measuring the refractive index of the solution, the hydrogen peroxide concentration is found from the relevant tables.

This method in addition to the volumetric ones can be used at pharmacies for controlling the quality of drugs.

In medicinal practice, hydrogen peroxide is used externally as an antiseptic. Its antiseptic effect is due to its oxidizing properties. When applied to a wound, hydrogen peroxide decomposes and evolves oxygen in the presence of an enzyme—the catalase of the blood. The vigorous evolution of oxygen looks like a foam. Hydrogen peroxide is employed to arrest the bleeding of wounds.

The properties of hydrogen peroxide determine the conditions for its storage—in orange glass bottles. The glass must have a negative test for alkalinity. The bottles should be closed with wax-coated or glass stoppers. The preparation should be stored in a cool place protected from light. Concentrated solutions are still more unstable, therefore perhydrol is stored in bottles coated inside with wax (a rough surface can accelerate the decomposition of the hydrogen peroxide). The bottles are usually kept in boxes with sawdust or sand.

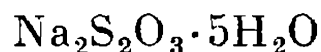
4.2. SULPHUR COMPOUNDS

Sulphur is an essential element in the human organism. It is contained in the epidermis, muscles, pancreas, and hair. Sulphur enters the composition of certain amino acids and peptides (cysteine, glutathione) that participate in tissue breathing and catalyze enzyme processes. Sulphur promotes the deposition of glycogen in the liver and lowers the sugar level in the blood.

Precipitated sulphur (*Sulfur praecipitatum*) is the official sulphur preparation. It is a pale yellow fine amorphous powder having no odour and insoluble in water. It is administered in the form of 5%, 10%, and 20% ointments as a mild irritant and antimicrobial agent in the treatment of skin diseases.

Sulphur compounds (such as $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ and $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$) are employed as laxatives. Another sulphur compound used in medicine is sodium thiosulphate—a detoxicating and desensitizing agent.

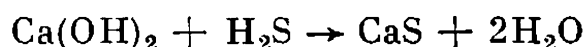
Sodium Thiosulphate (*Natrii thiosulfas*)



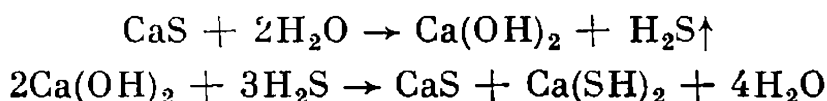
M.m. 248.17

Sodium thiosulphate is not a natural product, it is synthesized. It is produced commercially from the residues of the gas industry. This method, notwithstanding its multiple-stage nature, is profitable economically because it utilizes the residues of gas production and, particularly, the lighting gas formed in the coking of coal.

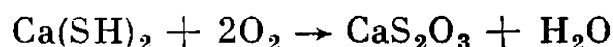
Lighting gas always contains an admixture of hydrogen sulphide, which is trapped by absorbents such as calcium hydroxide. The product is calcium sulphide:



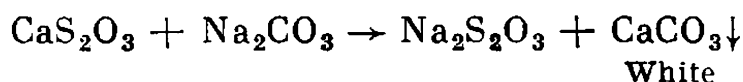
But the calcium sulphide in the course of its formation becomes hydrolyzed, therefore the reaction proceeds somewhat differently, with the formation of calcium hydrosulphide:



The calcium hydrosulphide is oxidized by the oxygen of the air to calcium thiosulphate:

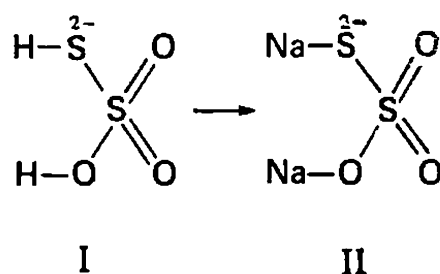


Fusion of the calcium thiosulphate with sodium sulphate or carbonate yields sodium thiosulphate $\text{Na}_2\text{S}_2\text{O}_3$:



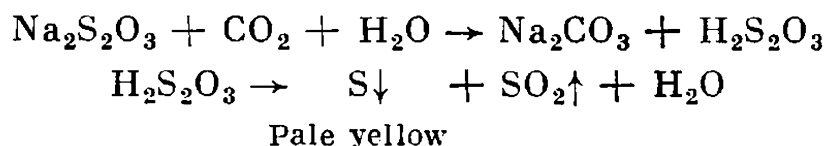
Evaporation of the solution produces crystals of sodium thiosulphate, a pharmacopoeial preparation.

Sodium thiosulphate(II) forms colourless transparent crystals with a bitter salty taste. It dissolves very readily in water. At 50 °C, it melts in its crystallization water. In its structure, it is a salt of thiosulphuric acid (I):

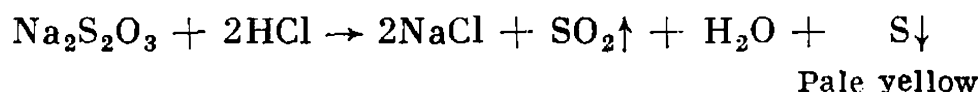


A glance at the formulas of these compounds reveals that the oxidation state of sulphur atoms in their molecules varies. One sulphur atom has an oxidation state of +6, and the other of -2. The presence of sulphur atoms in different oxidation states explains the properties of these compounds. Having S^{2-} in a molecule, sodium thiosulphate exhibits reducing properties.

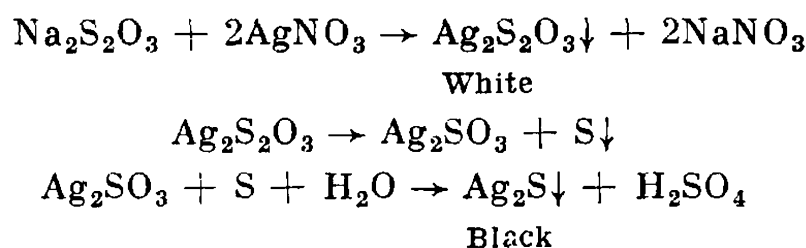
Like thiosulphuric acid itself, its salts are not stable and readily decompose under the influence of acids, and even of such weak ones as carbonic acid:



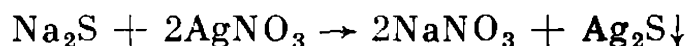
This property of sodium thiosulphate to be decomposed by acids with the precipitation of sulphur is employed for identification of the preparation. When hydrochloric acid is added to a sodium thiosulphate solution, turbidity of the solution is observed owing to the precipitation of sulphur:



A specific reaction of sodium thiosulphate is that with a silver nitrate solution. A white precipitate (silver thiosulphate) appears that rapidly turns yellow. When left standing, the precipitate becomes black under the influence of the atmospheric moisture owing to the evolution of silver sulphide:

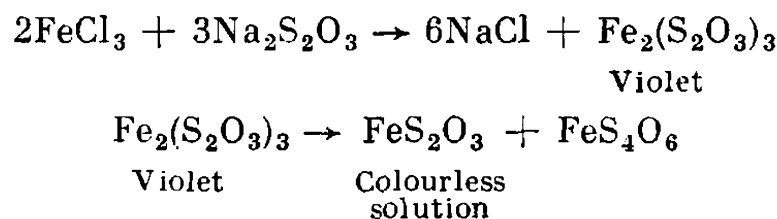


Should a black precipitate form immediately after sodium thiosulphate has reacted with silver nitrate, the preparation is contaminated by sulphides; the latter react with the silver nitrate and a silver sulphide precipitates:

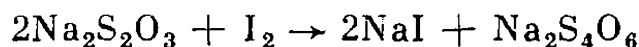


The pure preparation when reacted with a silver nitrate solution does not turn black immediately.

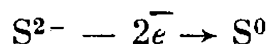
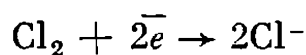
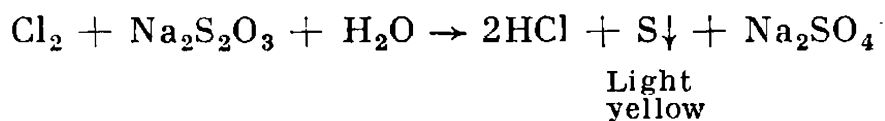
The reaction of sodium thiosulphate with an iron(III) chloride solution can also be used as an identification reaction. A product is violet iron(III) thiosulphate. The colour rapidly disappears because of the reduction of this salt to colourless iron(II) salts (FeS_2O_3 and FeS_4O_6):



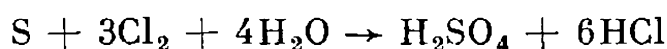
Sodium thiosulphate is a reducing agent when it reacts with iodine. The iodine accepts electrons from the S^{2-} and is reduced to I^- , while the sodium thiosulphate is oxidized by the iodine to sodium tetrathionate:



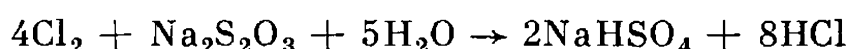
Chlorine is reduced to hydrogen chloride by sodium thiosulphate:



With an excess of chlorine, the evolved sulphur is oxidized to sulphuric acid:



The overall reaction is:

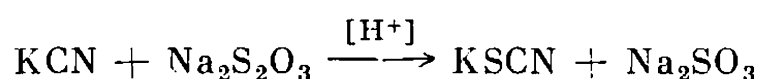


The use of sodium thiosulphate to absorb chlorine in the first gas masks was based on this reaction.

The preparation must not contain admixtures of arsenic, selenium, carbonates, sulphates, sulphides, sulphites, and calcium salts. The State Pharmacopoeia allows admixtures of chlorides and salts of heavy metals within the limits of the standard.

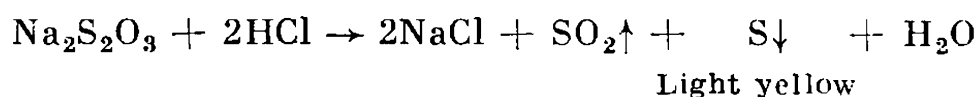
Sodium thiosulphate is determined quantitatively by the iodimetric method based on its reaction with iodine. The State Pharmacopoeia requires a sodium thiosulphate content of at least 99% and at most 102% of the indicated amount (owing to the tolerated limits of weathering of the preparation).

The use of sodium thiosulphate is based on its property of evolving sulphur. The preparation is employed as an antidote in poisoning by halogens, cyanogen, and hydrocyanic acid:



The formed potassium thiocyanate is much less poisonous than potassium cyanide. This is why sodium thiosulphate should be taken as first aid in poisoning by hydrocyanic acid or its salts. The preparation can also be used in poisoning by arsenic, mercury, and lead compounds, because it converts them into non-poisonous sulphides.

M. Demyanovich proposed using the reaction of sodium thiosulphate with hydrochloric acid to heal itch. The formed finely dispersed sulphur and the sulphur dioxide that has a high parasitocidal effect stop the itching and kill the itch mite:



Sodium thiosulphate is administered intravenously in allergic diseases, arthritides, and neuralgia in the form of a 30% aqueous solution. The State Pharmacopoeia indicates a 30% sodium thiosulphate

solution for injections (*Solutio Natrii thiosulfatis 30% pro injectionibus*). The preparation is available in powders and in ampoules containing 5, 10, or 50 ml of a 30% solution.

Sodium thiosulphate contains crystallization water that readily weathers, therefore it should be stored in a cool place in well closed dark glass bottles because light facilitates its decomposition. Stored solutions with time become turbid because of the evolution of sulphur. This process is accelerated in the presence of carbon dioxide. This is why stoppers in bottles with sodium thiosulphate solutions are provided with a calcium chloride tube filled with soda lime that absorbs CO_2 .

REVIEW QUESTIONS

1. How can the non-metallic nature of the oxygen subgroup elements be explained?
2. Why does oxygen exhibit a negative valence of two in most compounds?
3. What are the increased requirements to the purity of oxygen due to?
4. What underlies the quantitative determination of oxygen?
5. Why are the cocks of cylinders containing oxygen coated with talc instead of grease?
6. What are the chemical properties of hydrogen peroxide?
7. In what two ways does hydrogen peroxide decompose?
8. What properties of hydrogen peroxide are used for its identification?
9. For what purpose is ether added when hydrogen peroxide is identified by reacting it with potassium dichromate?
10. What colour does the ether layer acquire and why?
11. How can the green colour of the water layer be explained?
12. What properties of hydrogen peroxide are employed for performing its quantitative analysis?
13. What requirements must the storage of hydrogen peroxide meet and why?
14. What are the chemical properties of sodium thiosulphate and what are they due to?
15. Why does sodium thiosulphate first produce a white precipitate and then a black one when reacted with a silver nitrate solution? Write the equations of the reactions.

PRACTICAL LESSON

Analysis of a 3% Hydrogen Peroxide Solution

1. Carry out an identification reaction.
To 1 ml of the analyte solution add 1 ml of dilute sulphuric acid, 1 ml of ether, and 0.5 ml of a potassium dichromate solution: the ether layer acquires a blue colour. Write the equation of the chemical reaction.
2. Perform a quantitative determination (by the permanganatometric method).
Put 10 ml of the analyte solution into a 100-ml measuring flask, add water up to the mark, and thoroughly stir. Transfer 20 ml of the diluted solution into a flask for titration, add 5 ml of a sulphuric acid solution, and titrate with a 0.1 N potassium permanganate solution until a pale pink colour appears. Write the equation of the chemical reaction.

3. Calculate the content of hydrogen peroxide in per cent in the solution by formula (1.2):

$$X = \frac{VKTV_1}{aV_2} \times 100 = \frac{VK \times 0.0017 \times 100}{10.0 \times 20.0} \times 100$$

where V is the volume of the 0.1 N potassium permanganate solution, ml, $T = 0.0017$ g/ml, and a is the volume of the preparation taken for the determination.

The content of H_2O_2 in the preparation should be 2.7-3.3% (State Pharmacopoeia).

4. Conclude whether hydrogen peroxide has actually been submitted for analysis, what its content in per cent is, and whether it corresponds to the requirements of the State Pharmacopoeia and can be dispensed.

5. Propose other possible methods for the quantitative determination of hydrogen peroxide. Write the equations of the reactions.

Analysis of Distilled Water

Control the quality of distilled water with respect to all the indices in accordance with the official requirements.

Chapter 5. Group VA Elements

The Group VA elements including nitrogen, phosphorus, arsenic, antimony, and bismuth are of interest for medicine. The outer layer of an atom of these elements has five electrons, therefore their ability to attach electrons is much weaker than that of the elements of Groups VIA and VIIA. On the other hand, the Group VA elements donate electrons more readily than those of Groups VIA and VIIA, and therefore their oxygen compounds are more stable.

Consequently, the Group VA elements exhibit both a positive and negative oxidation states. The highest positive oxidation state of these elements is $+5$, and the negative one is -3 .

Owing to the relatively lower electronegativity, the bond of the given elements with hydrogen is less polar than that of Group VIA and VIIA elements. As a result, the hydrogen compounds of the elements being considered do not detach hydrogen ions in an aqueous solution and consequently have no acidic properties.

5.1. NITROGEN COMPOUNDS

The nitrogen compounds employed in medicine include an aqueous ammonia solution, ammonium salts, nitrous oxide, and sodium nitrite. The latter two are described in the State Pharmacopoeia.

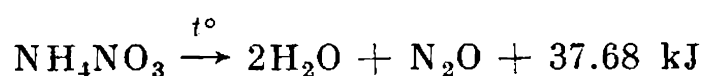
Nitrous Oxide (*Nitrogenium oxydulatum*)



N_2O

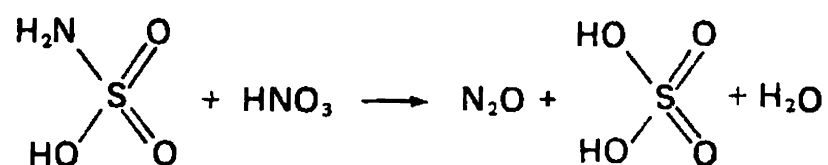
M.m. 44.01

Nitrous oxide (dinitrogen oxide or “laughing gas”) was discovered by J. Priestley (1776). It is prepared by the thermal decomposition of ammonium nitrate. Decomposition of the salt begins at 190 °C following the reaction



The nitrous oxide obtained in this way contains nitrogen oxides as impurities. The latter are removed by passing the gas through a number of absorbents.

Purer nitrous oxide can be produced by heating sulphamic acid with a 73% nitric acid solution:



Nitrous oxide is a colourless gas heavier than air with a characteristic odour and a sweetish taste. It supports combustion. A glowing splinter introduced into nitrous oxide ignites with a bright flame. This property of nitrous oxide can be used to identify it.

To distinguish nitrous oxide from oxygen, which also supports combustion, equal volumes of it and nitric oxide are mixed, and no red smoke should appear (State Pharmacopoeia). Nitrous oxide dissolves well in water.

The inhalation of small amounts of nitrous oxide dulls the sensitivity to pain, which explains its use (mixed with oxygen) as an anaesthetic.

Large amounts of nitrous oxide have a stimulating effect on the nervous system, which explains its commonly used name “laughing gas”. Nitrous oxide is more volatile than other substances with a similar action (ether, chloroform). It is rapidly excreted from the organism, thus producing less side effects. This is its advantage over other anaesthetics.

Since nitrous oxide is used for anaesthesia, it must be free of any possible impurities including carbon dioxide, hydrogen arsenide, phosphide, and sulphide, halogens, oxidizing and reducing substances, bases and acids. These impurities are detected by passing the nitrous oxide being analysed through a number of absorber bottles with water to which the relevant reagents have been added that give a characteristic reaction with one of the impurities. For example, ba-

ryta water becomes turbid in the presence of CO_2 , a silver nitrate solution produces opalescence in the presence of halides, a potassium permanganate solution loses its colour when reducing substances are present in the oxide, and so on.

Moreover, nitrous oxide may be contaminated with uncondensed gases (nitrogen oxides, ammonia) that are determined quantitatively with the aid of a special instrument.

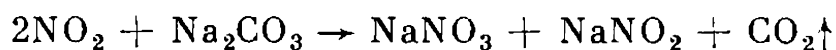
Nitrous oxide is liquefied under a pressure of 150-225 atm and is poured into steel cylinders. It is stored in cylinders with a capacity of 10 litres, coloured gray, at a pressure of 30 atm. When the cock is opened, the nitrous oxide escapes and transforms into the gaseous state. It is fed into rubber bags, from which it is inhaled by patients. Nitrous oxide should always be administered in a mixture with oxygen (up to 20-25%), because in the pure state it rapidly causes asphyxia.

Sodium Nitrite (*Natrii nitris*)

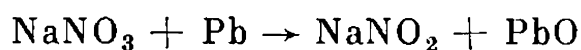
NaNO_2

M.m. 69.00

The industrial production of sodium nitrite is associated with the production of nitric acid. The nitrogen oxide formed in the production of nitric acid is converted to the dioxide NO_2 , which is absorbed by sodium carbonate (or an alkali) to form sodium nitrate and nitrite:



After the nitrite has been separated by fractional recrystallization, the nitrate can be used to produce the nitrite by reducing it with lead:



When the sodium nitrite has been purified from possible admixtures (chlorides, sulphates, heavy metals, arsenic) until their content is within the tolerated value, the preparation is allowed to be used.

Sodium nitrite is a white crystalline substance with a pale yellow tint. It readily dissolves in water, forming solutions with a weakly alkaline reaction. It dissolves sparingly in alcohol. It is hygroscopic.

The oxidation state of the nitrogen in sodium nitrite is +3, i.e. it is intermediate between the lower and higher (+5) oxidation states of nitrogen. Consequently, sodium nitrite exhibits an oxidizing and reducing properties. They are illustrated by the following reactions:

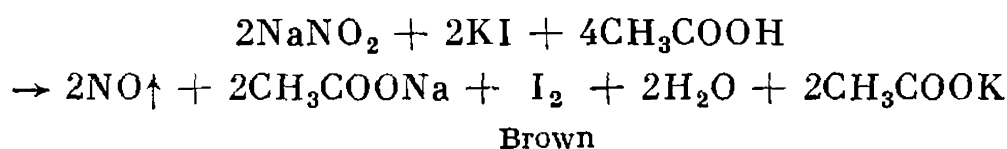


Violet

Colourless
solution

In this reaction, the sodium nitrite is a reducing agent.

In reactions with bromides and iodides in an acidic medium, sodium nitrite exhibits oxidizing properties (it oxidizes the iodide ion, for example, to molecular iodine):

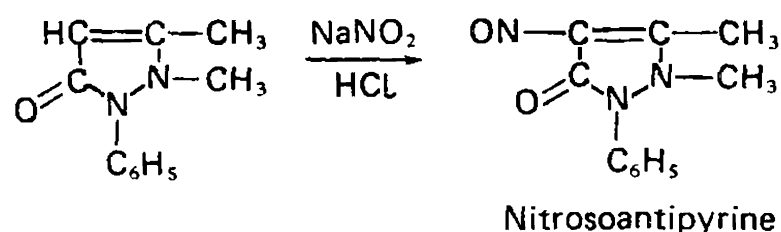


These reactions can be employed to identify the preparation, although they are not pharmacopoeial ones.

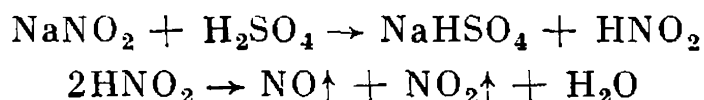
To identify sodium nitrite, the State Pharmacopoeia recommends the reactions of detecting the sodium ion (see the reactions of identification of sodium halides, p. 67) and the nitrite ion. The latter is detected by:

(a) a reaction with diphenylamine in an acidic medium to form an organic bright blue dye (see the reactions for determining impurities in distilled water, p. 80);

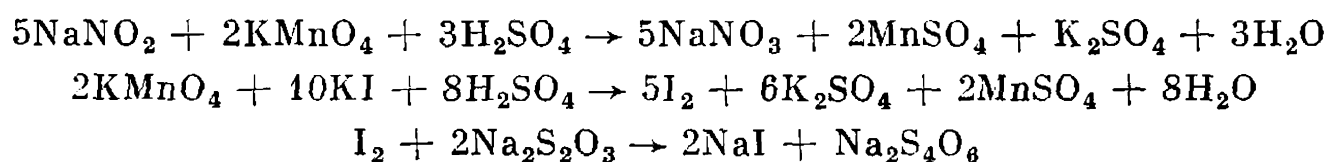
(b) a reaction with antipyrine in an acidic medium with the formation of nitrosoantipyrine imparting an emerald green colour to the solution:



(c) the evolution of red-brown nitrogen oxide vapour when dilute sulphuric acid is added to a sodium nitrite solution:



The content of the preparation is determined by iodimetry. The sodium nitrite is oxidized by potassium permanganate, the excess of which is determined iodimetrically (the pharmacopoeial method):



Sodium nitrite is taken orally or subcutaneously as a vasodilator in angina pectoris and migraine. It is generally available for subcutaneous injections in ampoules in the form of a 1% solution.

Sodium nitrite is also used as an antidote in cyanide poisoning. In this case, it is introduced intravenously in the form of a 1% solution up to 5 ml. Nitrites are very poisonous if taken in large amounts.

The preparation should be stored with care. It is hygroscopic and readily oxidizes in the air and in the light, therefore it should be stored in well closed orange glass jars in a dry and dark place. The drug is listed in Group B.

5.2. ARSENIC COMPOUNDS

Arsenic has been known to mankind from ancient times. Already in the 8th century its compounds were known to Arabian chemists, while in the 9th century Avicenna described arsenous anhydride in his works.

T. Paracelsus was the first to use arsenic compounds for medicinal purposes. Arsenic and its compounds in small doses are valuable drugs having a tonic effect on an organism. They increase metabolism and improve the state of an organism.

In the free state, arsenic is rarely encountered and in very insignificant amounts. Thus, it is contained in negligibly small amounts in animal and plant organisms and in the Earth's crust (about 0.0005%). It is found most often in nature in the form of its sulphur compounds, namely, realgar (red arsenic) As_2S_2 and orpiment As_2S_3 , and also in the form of compounds with many metals—iron, cobalt, nickel, copper, and silver. Among them, arsenic is encountered most frequently in the form of mispickel (sulpharsenide of iron) $\text{Fe}_2\text{As}_2\text{S}_2$, and the arsenic is produced by roasting the latter without the access of air.

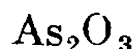
Metallic arsenic is a silvery gray substance with a typical metallic lustre. Arsenic burns in air with a blue flame to form arsenous oxide As_2O_3 having a characteristic smell of garlic. Arsenic forms two oxides, As_2O_3 and As_2O_5 , in which it has a positive oxidation state of +3 and +5, respectively. Both As(III) and As(V) compounds are pharmacological preparations. Arsenous anhydride As_2O_3 , often called white arsenic, is such a preparation.

Two acids correspond to arsenic(III) oxide, namely, ortho-arsenous H_3AsO_3 and meta-arsenous HAsO_2 acids. Their salts are called arsenites.

A solution of potassium arsenite KAsO_2 called **Fowler's solution** is used in medicine. This preparation, like arsenous anhydride As_2O_3 , is described in the State Pharmacopoeia.

Arsenic acid H_3AsO_4 corresponds to arsenic(V) oxide As_2O_5 . Its disubstituted salt, sodium arsenate $\text{Na}_2\text{HAsO}_4 \cdot 7\text{H}_2\text{O}$ is a pharmacopoeial preparation.

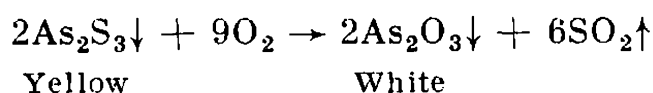
Arsenous Anhydride (*Acidum arsenicosum anhydricum*)



M.m. 197.84

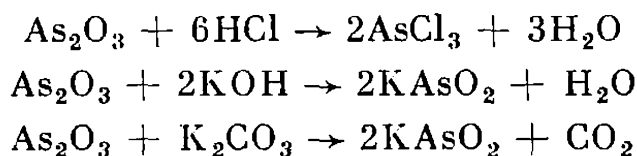
Arsenous anhydride is rarely found in the free state because it is readily oxidized.

It is prepared by roasting the sulphur compounds of arsenic generally found in nature in a stream of air:



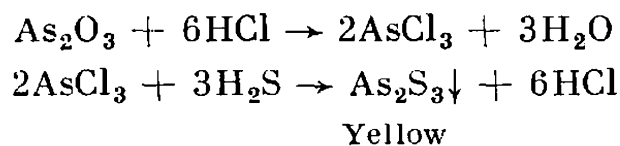
The arsenous anhydride is purified by sublimation. Depending on the temperature at which the sublimation is carried out, two modifications of the anhydride can be obtained, namely, a vitreous and a porcelain-like ones. The vitreous form of the anhydride is obtained when sublimation is performed at 200-300 °C. At lower sublimation temperatures, the porcelain-like form is obtained. These two modifications can transform into each other.

Arsenous anhydride forms heavy white porcelain-like or vitreous pieces, and sometimes a heavy white powder. It dissolves very slowly in water, readily in hydrochloric acid, and in solutions of alkalis and alkali metal carbonates. This indicates that it is an amphoteric oxide:

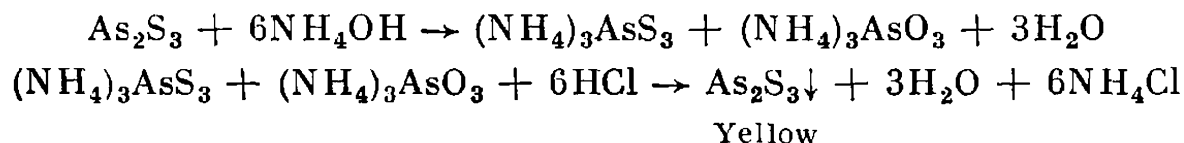


When heated, arsenous anhydride sublimes and settles on the walls of the test tube in the form of white very minute transparent crystals.

When arsenous anhydride is reacted with sodium sulphide in an acidic medium, a yellow precipitate or gel of arsenic(III) sulphide forms:



The arsenic(III) sulphide readily dissolves in an ammonia solution, in alkali metal hydroxides, and concentrated nitric acid, and is insoluble in hydrochloric acid:



These reactions are used to identify the preparation and are pharmacopoeial ones. Other reactions can also be used to identify the preparation:

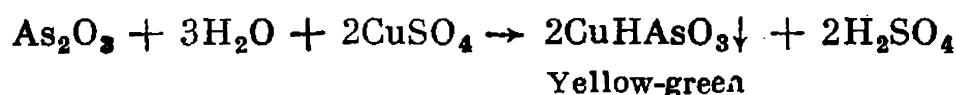
(a) an iodine solution oxidizes As(III) to As(V); the solution loses its colour owing to the reduction of the I_2 to HI:



To prevent the reverse reaction, sodium bicarbonate is added to neutralize the formed hydroiodic acid:



(b) copper salts (a copper sulphate solution) when added to an arsenous anhydride solution form a yellow-green precipitate of $CuHAsO_3$ (Scheele's green):

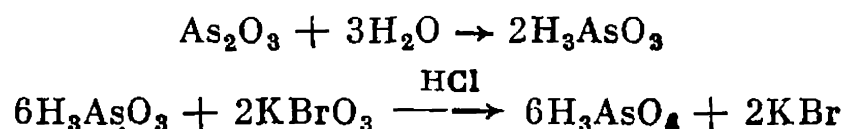


The precipitate dissolves in an excess of an alkali to form a light blue solution; when the latter is heated, red copper(I) oxide Cu_2O precipitates.

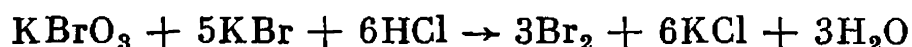
An admixture of arsenic(III) sulphide As_2S_3 is not tolerated in the preparation. To detect such an impurity, the preparation is dissolved in ammonia, and if it contains arsenic(III) sulphide a transparent solution of soluble thiosalts forms. The addition of a mineral acid to this solution causes a yellow precipitate to appear.

Arsenous anhydride is determined quantitatively in the preparation either by the bromatometric (State Pharmacopoeia) or iodimetric method. Both methods take advantage of the oxidation of As(III) to As(V).

In bromatometry, the arsenous anhydride is titrated with a potassium bromate solution in an acidic medium using a methyl red indicator until the solution loses its colour:



At the equivalence point, an excess drop of the solution of potassium bromate $KBrO_3$ evolves free bromine which decolorizes the indicator:



In iodimetry, arsenous anhydride is titrated with a 0.1 *N* iodine solution in the presence of sodium bicarbonate. The amount of iodine used for titration allows one to find the content of the arsenous anhydride.

Arsenous anhydride is administered externally and orally. It is used externally to treat certain skin diseases. In stomatology, it is

employed for necrosis of the pulp. It is prescribed in pills for treating anaemia, emaciation, and neurasthenia. It is included in the composition of Blaud's pill with arsenic. The highest tolerated single dose for adults taken orally is 0.005 g, and the highest daily dose is 0.015 g.

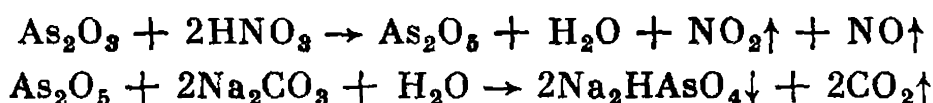
It is stored locked up in well closed bottles labelled "Poison". It is listed in Group A.

Sodium Arsenate (*Natrii arsenas*)



M.m. 312.01

Sodium arsenate is produced by oxidizing arsenic(III) oxide to arsenic(V) oxide, which is then treated with sodium carbonate. Generally nitric acid is used as the oxidizing agent. It is reduced to volatile nitrogen oxides, and the main product of the reaction is purer:



Sodium arsenate forms colourless, odourless crystals that readily weather in the air. Weathered crystals acquire a dull appearance. It dissolves well in water, better in hot water. It dissolves slightly in alcohol. Aqueous solutions have an alkaline reaction to litmus.

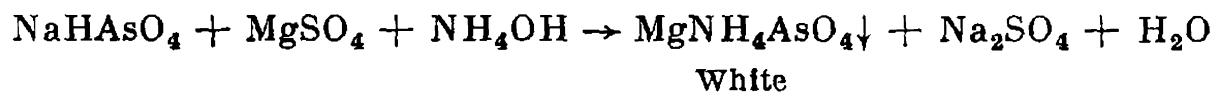
The drug is identified by the following reactions:

(a) with a silver nitrate solution; when the latter is added to a solution of the drug, dark brown silver arsenate precipitates (unlike As^{3+} , when the precipitate is yellow):



The precipitate dissolves in a solution of ammonia and nitric acid;

(b) with a magnesia mixture; when a solution of a magnesium salt (for example, MgSO_4), and a solution of ammonia and ammonium chloride are added to a solution of the drug, a finely crystalline white precipitate of magnesium and ammonium arsenate $\text{MgNH}_4\text{AsO}_4$ forms:

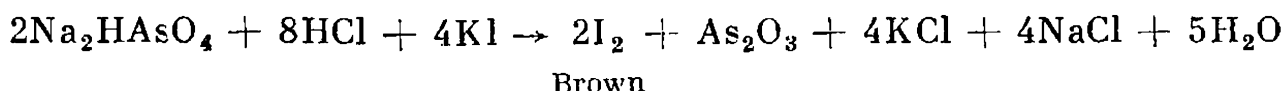


These two reactions are official ones.

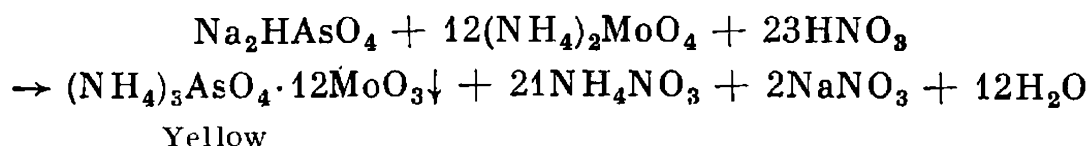
In addition to the above reactions, other identification reactions can be used, for example:

(1) an iodine solution does not lose its colour when added to a solution of the drug, which does occur when it is added to compounds of arsenic(III);

(2) a solution of the drug when potassium iodide is added in an acidic medium becomes brown owing to the evolution of free iodine:

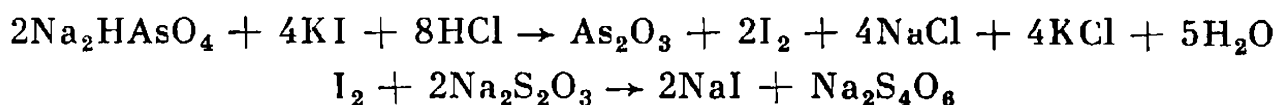


(3) when a solution of the drug is reacted with an ammonium molybdate solution in the presence of nitric acid with heating, a yellow crystalline precipitate of ammonium arsenomolybdate appears:



The proper quality of the drug is determined by the absence of admixtures of carbonates, nitrates, and arsenites. Admixtures of chlorides and sulphates are tolerated in an amount not exceeding the standard. These impurities are detected by the reactions customarily employed for this purpose.

The content of sodium arsenate in the drug is determined by iodimetry (State Pharmacopoeia). The method is based on the ability of As(V) to reduce to As(III):



The drug is used in the form of a 0.5-1.0% aqueous solution for subcutaneous injections (*Solutio Natrii arsenatis 1% pro injectionibus*), which is a colourless odourless liquid.

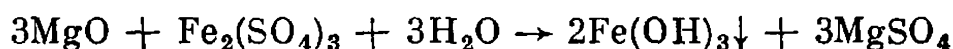
It is employed as a general tonic and for stimulating haemopoiesis (blood formation) in emaciation, anaemia, and neurosis. The highest single subcutaneous dose is 0.01 g, the highest daily dose is 0.2 g. It is stored in a locked cupboard. It is listed in Group A.

Since the drug contains crystallization water, it is very important to ensure proper storage conditions to prevent weathering of the water. Otherwise the arsenic content in a dose will grow, which may cause poisoning.

5.3. ARSENIC ANTIDOTE

All arsenic compounds are very poisonous. Arsenic poisoning results in a sharp collapse, muscular weakness, and in the long run paralysis and death. In acute arsenic poisoning, apomorphine is given subcutaneously as an emetic, and gastric lavage is used. A preparation called arsenic antidote (*Antidotum Arsenici*) can be employed. It is a mixture of burnt magnesia and iron(III) sulphate. These substances are kept separately in a pharmacy and are poured to-

gether when needed. The reaction of these two substances form iron(III) hydroxide $\text{Fe}(\text{OH})_3$ and magnesium sulphate MgSO_4 :



It is exactly the freshly precipitated iron hydroxide that is the antidote because with arsenic it forms iron(III) arsenite FeAsO_3 —a compound insoluble in the gastric juice. Moreover, the freshly precipitated iron hydroxide adsorbs arsenic compounds, while the magnesium sulphate formed in the reaction acts as a purgative and facilitates the excretion of the poison from the organism. This is why it is recommended to prepare this antidote *ex tempore* because only freshly precipitated iron hydroxide has adsorbing properties.

A more effective means in arsenic poisoning is the antidote against metals (*Antidotum metallorum*). It is a supersaturated alkaline solution of hydrogen sulphide in water with the addition of magnesium sulphate. The preparation is dispensed in 100-ml bottles. Its composition (in grammes) is H_2S —0.5-0.7, NaOH —0.1, NaHCO_3 —1.25, and MgSO_4 —0.38.

The mechanism of action of this antidote consists in that the reagent forms insoluble compounds with arsenic, and therefore these precipitates are not absorbed by the organism. In acute arsenic poisoning, the administration of this antidote is preceded by giving 3 g of citric or 4 g of tartaric acid, or 1.5 tablespoons of vinegar essence diluted in 300 ml of water. It is recommended to drink albumin water in this case.

5.4. REACTIONS FOR DETECTING ARSENIC ADMIXTURES IN DRUGS

Arsenic is very often an exceedingly undesirable admixture in drugs. It may get into drugs from the material of the apparatus used in the production of the relevant preparation, or together with the raw material, solvents, etc.

Owing to the very poisonous nature of arsenic and its admixtures, special sensitive reactions are employed to detect insignificant amounts of arsenic in medicinal preparations regardless of its oxidation state.

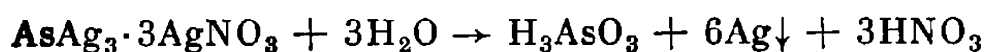
Among the existing tests for detecting admixtures of arsenic in drugs, the Gutzeit, Bougeau, and Thiele tests have found the greatest use in pharmaceutical analysis. They are based on the ability of arsenic to be reduced from its compounds either to free arsenic forming an amorphous brown precipitate (the Bougeau and Thiele test), or to hydrogen arsenide (arsine), which is detected by the formation of complexes with a solution of silver nitrate or mercury dichloride having a characteristic colour (the Gutzeit test).

Gutzeit test. The drug assumed to contain arsenic as an impurity is placed in a test tube, and metallic zinc and a dilute mineral acid are added to it. The evolving hydrogen reduces the arsenic to hydrogen arsenide AsH_3 . The test tube is covered with filter paper wetted with a silver nitrate solution.

The formed hydrogen arsenide reacts with the silver nitrate to form a complex producing a yellow spot on the paper. Moisture causes the complex to decompose with the evolution of free silver that darkens the filter paper:



Yellow



Black

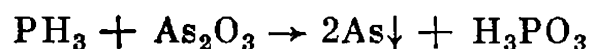
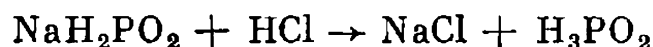
The Gutzeit test has a number of limitations, however. It cannot be used for drugs which in addition to admixtures of arsenic are presumed to contain antimony, phosphorus, or mercury and silver, because under these conditions they will also be reduced and mask the detection of arsenic.

Moreover, a silver nitrate solution has a low stability with respect to light and moisture. All this made it necessary to modify the Gutzeit test and use other reagents instead of silver nitrate.

The State Pharmacopoeia recommends a variant of the Gutzeit test modified by F. Fluckiger, P. Lehmann, and V. Skvortsov. The filter paper is impregnated with an alcohol solution of mercury dichloride that reacts with hydrogen arsenide to form the complex $\text{As}(\text{HgCl})_3 \cdot \text{Hg}_2\text{Cl}_2$. The latter colours filter paper orange red.

The use of a mercury dichloride solution makes the test more sensitive and enables one to detect thousandths of a milligramme of arsenic.

Bougeau and Thiele test. In this test, arsenic compounds are reduced to elementary arsenic by sodium hypophosphite in an acidic medium with heating. Depending on the arsenic concentration, a brown precipitate or a dark brown liquid forms:



Brown

This test, although it is less sensitive than the preceding one (the maximum sensitivity of the reaction is 0.01 mg of arsenic in 10 ml of the reaction mixture), can be used to detect arsenic in the presence of compounds of antimony, phosphorus, lead, and of sulphides, which are not reduced by hypophosphorous acid.

REVIEW QUESTIONS

1. Explain why Group VA elements can exhibit both positive and negative oxidation states.
2. Why do the hydrogen compounds of Group VA elements have no acidic properties?
3. How can nitrous oxide be distinguished from oxygen?
4. Why does sodium nitrite run in the air? Explain this phenomenon from the chemical viewpoint.
5. What are the requirements for the storage of sodium nitrite and why are they needed?
6. What causes the indicator (methyl red) to lose its colour in the bromatometric determination of arsenous anhydride?
7. What can happen to the crystallization water when storing sodium arsenate?

PRACTICAL LESSON

Analysis of a 10% Solution of Sodium Thiosulphate

1. Perform identification reactions.
 - (a) Add two or three drops of a silver nitrate solution to 1 ml of a solution of the preparation; a white precipitate forms that rapidly turns yellow, then brown, and finally black;
 - (b) add a solution of hydrochloric acid to 2-3 ml of a solution of the preparation: a yellow precipitate forms.
 Write the equations of the chemical reactions.
2. Carry out a quantitative determination.

Transfer 10 ml of the preparation into a 100-ml measuring flask, add water up to the mark, and agitate the mixture. Transfer 10 ml of the diluted solution into an Erlenmeyer flask and titrate with a 0.1 *N* iodine solution up to a pale yellow colour.
3. Calculate the content of sodium thiosulphate in per cent in the solution by formula (1.2):

$$X = \frac{VKTV_1}{aV_2} \times 100 = \frac{VK \times 0.0248 \times 100}{10.0 \times 10.0} \times 100$$

where *V* is the volume of a 0.1 *N* iodine solution, ml, *T* = 0.0248 g/ml, and *a* is the volume of the preparation taken for the determination, ml.

4. Conclude whether the analyte solution is actually sodium thiosulphate, and establish its content in per cent.

Chapter 6. Group IIIA Elements

The Group IIIA elements include boron, aluminium, gallium, indium, and thallium.

The outer electron layer of an atom of these elements contains three electrons. Therefore the tendency to attach electrons to make up a stable layer of eight electrons is not characteristic of them. This is why they do not exhibit a negative oxidation state in their

compounds. The metallic properties of the elements being considered are expressed more weakly than in the corresponding elements of Group IIA and especially of Group IA, while boron mainly has non-metallic properties.

Boron, aluminium, gallium, and indium have an oxidation state of +3 in their compounds. However, the metallic properties of the elements in this group become more pronounced with an increase in their atomic mass and atomic number. Boron has clearly expressed non-metallic properties, while aluminium, gallium, and indium are metals with amphoteric properties. The metallic properties of thallium are still more pronounced. Among the Group IIIA elements, only boron and aluminium are of importance in medicine. Some of their compounds are used as drugs.

6.1. BORON COMPOUNDS

Boron is a quite widespread element in nature. It is contained in many minerals. It is found in nature chiefly in the form of oxygen compounds, the most abundant of which are boric acid and its various salts. The best known of the latter is borax, or tincal $\text{Na}_2\text{B}_4\text{O}_7 \cdot 10\text{H}_2\text{O}$.

Boron is one of the numerous microelements playing a definite physiological role. It is known that boron metabolism is to some extent associated with that of potassium.

Boron compounds are used in medicine in the form of boric acid and borax, which have a disinfecting action.

Boric Acid (*Acidum boricum*)

H_3BO_3 M.m. 61.83

Boric acid is produced commercially from boron-containing minerals (for example, ascharite $\text{Mg}_2\text{B}_2\text{O}_5 \cdot \text{H}_2\text{O}$) by reacting them with concentrated sulphuric acid:



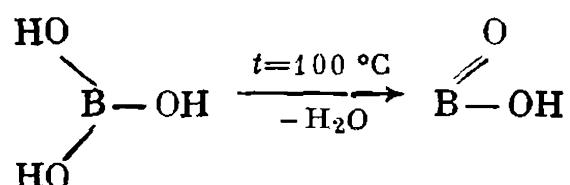
This boric acid is contaminated with admixtures of sulphates of the elements accompanying the boron minerals (sulphates of calcium, magnesium, aluminium, iron, etc.) and requires purification.

Boric acid yields sparingly soluble salts with all cations except the alkali metals. These metals, depending on the conditions, react with boric acid to form various borates, the most significant of which are metaborates of the type MeBO_2 and disubstituted tetraborates $\text{Me}_2\text{B}_4\text{O}_7$. The latter include borax $\text{Na}_2\text{B}_4\text{O}_7 \cdot 10\text{H}_2\text{O}$, from

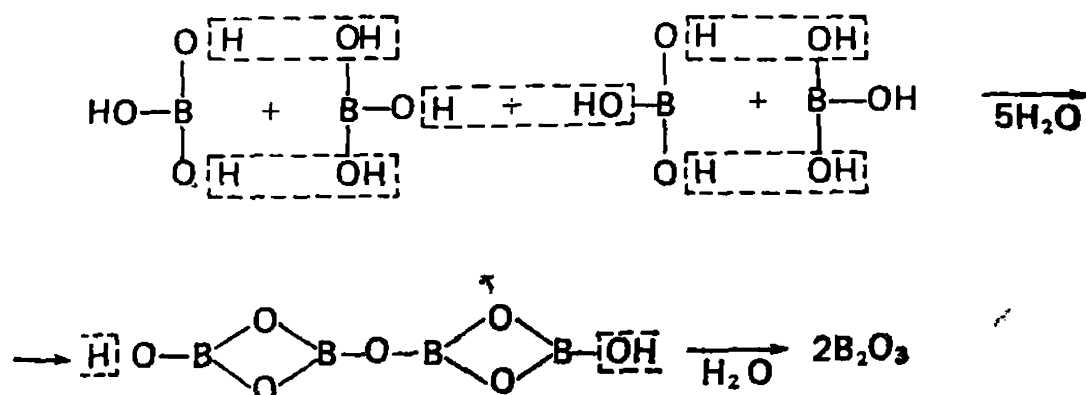
which boric acid is produced for medical purposes. To this end, a hot borax solution is treated with a mineral acid:



Pure boric acid forms colourless, transparent, flaky crystals feeling greasy, or a fine white crystalline powder without an odour. It dissolves poorly in cold water and well in hot water. It is soluble in alcohol (1:25) and slowly in glycerin (1:7). In prolonged heating up to 100 °C, boric acid loses part of its water and transforms into metaboric acid:

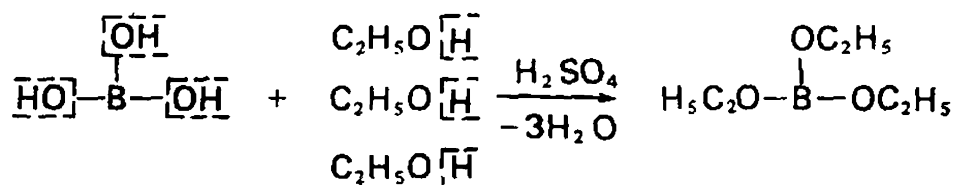


Heating to a higher temperature transforms the boric acid into tetraboric acid $\text{H}_2\text{B}_4\text{O}_7$, and after passing through the stage of a vitreous fused body, it loses all its water and transforms into boric anhydride:



When dissolved in water, all these compounds again transform into boric acid.

Many reactions exist for detecting boron in its compounds. They vary in their sensitivity and mainly use organic reagents. The most widespread is the reaction with alcohol in the presence of concentrated sulphuric acid (a water-removing agent). The product is triethyl borate, which burns with a flame having a green fringe:

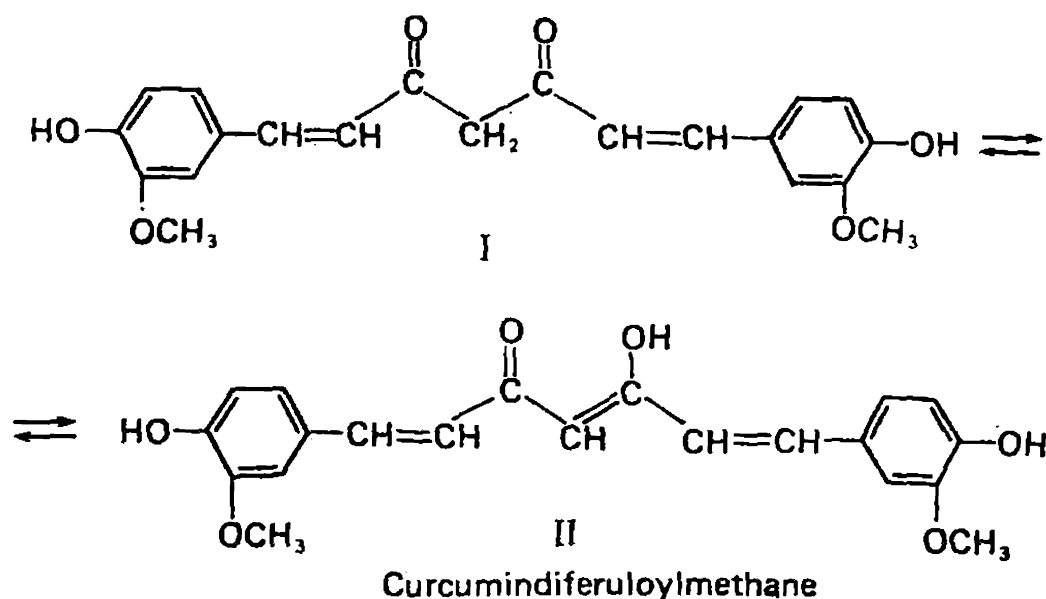


This reaction is an official one. Another way of detecting boron in its compounds is a reaction with curcumin, which was one of the first reagents to be used to detect boric acid.

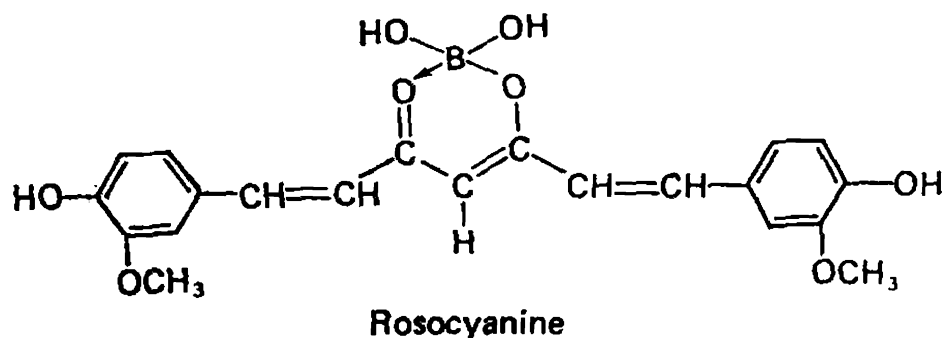
Curcumin is an organic substance prepared from an extract of the rhizome of *Curcuma domestica*. It is a yellow-orange crystalline substance. When dissolved in aqueous solutions of alkalies, a reddish-brown colour results; when the solution is acidified, it turns light yellow. Generally curcuma paper is used for the reaction. It is conventional filter paper impregnated with an alcoholic extract of curcumin and dried without the access of acid or ammonia vapour.

The boric acid solution to be analysed is applied onto curcuma paper along with a few drops of hydrochloric acid. A pink or brownish-red colour appears in the acidic medium depending on the boric acid concentration. The addition of an ammonia solution causes a greenish-black colour to appear.

The yellow dye curcumindiferuloylmethane contained in *Curcuma domestica* exists in two tautomeric forms:



Only the tautomer in the enol form (II) is presumed to directly enter into a complexing reaction with boron to form the red complex rosocyanine:



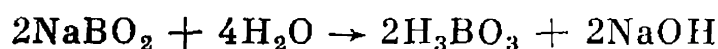
This reaction is also recommended by the State Pharmacopoeia for detecting boron in its compounds.

The determination of boron with curcumin is interfered with by elements like iron, molybdenum, and tungsten that react under the same conditions with curcumin to form similarly coloured complexes. This reaction is also interfered with by oxidizing agents that can oxidize the curcumin. The State Pharmacopoeia tolerates impu-

rities of calcium, iron, heavy metals, arsenic, and sulphates in the preparation in an amount not exceeding the standards. Pure boric acid should completely dissolve in hot water and alcohol.

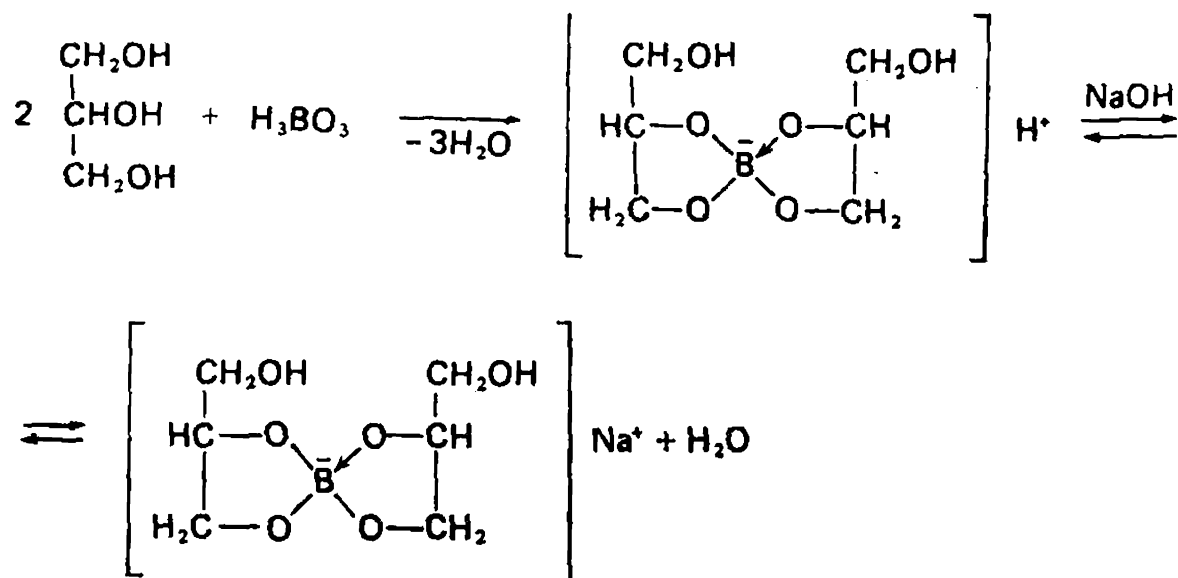
Of the chemical methods for the quantitative determination of boric acid, the greatest popularity has been won by the method of neutralization based on the titration with an alkali of the complexes of boric acid with polyatomic alcohols or sugars.

Boric acid is a very weak acid. Its dissociation constant is $K_1 = 6 \times 10^{-10}$ (at 20 °C); under these conditions, the equivalence point in the titration of boric acid with an alkali is at pH 11. In this region of the pH, it is difficult to find an indicator that would give a sharp change in colour. On the other hand, when alkalies react with boric acid, salts of tetraboric acid $H_2B_4O_7$ and in the long run of metaboric acid HBO_2 form instead of the expected salts of orthoboric acid H_3BO_3 . Consequently, if boric acid is titrated with an alkali, the formed salt of metaboric acid hydrolyzes:



As a result, the reaction of the solution becomes alkaline considerably before the equivalence point is reached. This is why direct titration of boric acid with an alkali with the required accuracy is almost impossible. To enhance the acidic properties of boric acid, it is reacted with polyatomic alcohols or sugars (glycerin, mannitol, dulcitol, sorbitol, etc.) to form complexes having stronger acidic properties than boric acid itself. These compounds can be titrated with the required accuracy in the presence of phenolphthalein.

The composition and properties of the glyceroboric complex have been studied better than those of mannitoboric ones, therefore the State Pharmacopoeia recommends the use of glycerin in titration. The predominating form of the glyceroboric complex in a solution is considered to be $HBGl_2$ (where HB stands for boric acid, and Gl for the glycerin residue), which is titrated with sodium hydroxide like a monobasic acid:

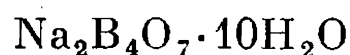


The obtained salt may hydrolyze. This causes the medium to become alkaline, and therefore the equivalence point is reached earlier than it should be. With this in view, the glycerin is added to the titration mixture at the end of titration. If the pink colour does not vanish, this indicates that the colour is due to an excess of the titrant, and not to hydrolysis. If the colour does vanish, it is necessary to add glycerin and continue titration.

In the quantitative determination of boric acid, freshly boiled water containing no carbon dioxide must be taken for dissolving the sample. The sodium hydroxide solution employed for titration must also be free of carbon dioxide because it can affect the change in the colour of the phenolphthalein. Boric acid should be titrated at room temperature because its complex with glycerin can decompose at a higher temperature.

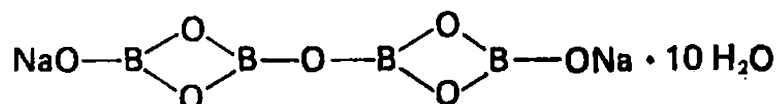
Boric acid has antiseptic properties, and this underlies its use in medicine. It is employed in the form of a 2-3% solution for gargling, in ointments and powders; 1-2% aqueous solutions are used in ophthalmology. Boric acid was previously used for preserving food products, but this is now prohibited because it has been established that boron compounds are poisonous. Boric acid requires no special conditions for its storage.

Sodium Tetraborate. Borax (*Natrii tetraboras. Borax*)

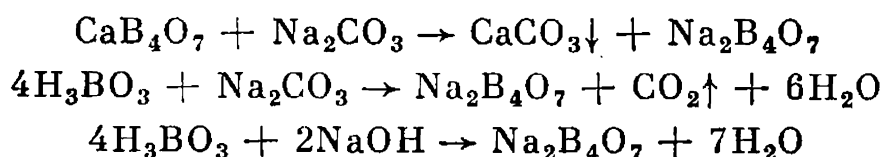


M.m. 381.37

Sodium tetraborate is encountered in nature in the free state as the mineral tincal, which is the sodium salt of tetraboric acid:



Sodium tetraborate, or borax, is produced from borocalcites or boric acid by reaction with an aqueous solution of sodium carbonate or sodium hydroxide:



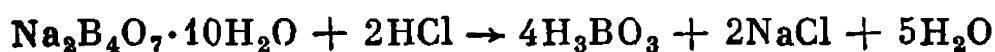
A crystalline powder can be obtained by concentrating a borax solution. When roasted, borax loses all its water and transforms into burnt borax (*Borax usta*).

The pharmacopoeial preparation of borax is colourless, transparent, readily weathering crystals or a white crystalline powder. Bo-

rax dissolves well in water, better when the latter is hot. It dissolves readily in glycerin and is insoluble in alcohol. Aqueous borax solutions have a strongly alkaline reaction owing to hydrolysis.

Borax participates in all the reactions characteristic of boric acid. Unlike the latter, it colours a flame yellow (Na).

Hydrochloric acid precipitates boric acid from a hot borax solution; the acid crystallizes out when the solution is cooled:



Borax must contain no admixtures of carbonates, while the admixtures of arsenic, chlorides, sulphates, and iron must not exceed the amounts indicated in the State Pharmacopoeia.

Borax is determined quantitatively by neutralization: it is titrated with a 0.1 *N* solution of hydrochloric acid using methyl orange as the indicator. The State Pharmacopoeia requires a borax content in a preparation of at least 99.5 and at most 103.0% of the stipulated amount.

Borax is employed like boric acid as an antiseptic in the form of 1-2% solutions.

The preparation should be stored in well closed jars in a cool place to prevent the weathering of the crystallization water.

REVIEW QUESTIONS

1. Why is sulphuric acid added in the reaction of formation of triethyl borate?
2. Can triethyl borate form when an alcohol reacts with a boric acid solution without the addition of concentrated sulphuric acid?
3. Why is glycerin added in the quantitative determination of boric acid? Write the equation of the chemical reaction. Determine the nature of the bonds in the formed compound.
4. What is the pH of glycerin and aqueous solutions of sodium tetraborate? What significance does this have in the preparation and dispensing of the drugs?

PRACTICAL LESSON

Analysis of Boric Acid

1. Perform identification reactions:
 - (a) wet curcuma paper with a solution of the preparation and several drops of 2 *N* hydrochloric acid; when the paper is dried a pink or brownish-red colour is observed that becomes greenish-black if the paper is wetted with an ammonia solution;
 - (b) an alcohol solution of the preparation burns with a flame having a green fringe.Write the equation of the chemical reactions.
2. Carry out a quantitative determination (the neutralization method).

Transfer a sample with a mass of 0.05 g into a conical flask for titration, dissolve it with slight heating in 20 ml of water, cool, add 5 ml of glycerin, 5 drops of phenolphthalein, and titrate with a 0.1 *N* solution of sodium hydroxide until a pink colour appears.

Write the equation of the chemical reaction.

3. Calculate the content of boric acid in the preparation in per cent by formula (1.1):

$$X = \frac{VKT}{a} \times 100 = \frac{VK \times 0.00618}{0.05} \times 100$$

where *V* is the volume of the 0.1 *N* sodium hydroxide solution, ml, and *T* = 0.00618 g/ml. The State Pharmacopoeia tolerates a content of H₃BO₃ of at least 99.5%.

Note. Transfer the sample into the flask only via a funnel; dissolve the sample either in hot water or with slight heating; before adding the glycerin and phenolphthalein, cool the solution (under a stream of cold water); titrate slowly drop by drop, and against a white background.

4. Having completed work, write the equations of the identification and quantitative determination reactions, and conclude that boric acid was indeed what was analysed.

Compare the content of the analysed boric acid with the requirements of the State Pharmacopoeia. Conclude whether it can be used to prepare drugs.

Analysis of Powders of 0.2 g of Sodium Tetraborate and 0.05 g of Sodium Chloride

1. Write the prescription in Latin.

2. Conduct a quantitative determination:

(a) Sodium chloride (Mohr's method):

transfer 0.1 g of the mixture into a titration flask, dissolve in 10 ml of hot water, cool the solution, add two drops of a potassium chromate solution and titrate with a 0.1 *N* silver nitrate solution until a flesh-coloured precipitate forms. Write the equations of the chemical reactions.

(b) Sodium tetraborate (the neutralization method):

transfer 0.1 g of the mixture into a titration flask, dissolve in 10 ml of hot water, cool the solution, add two drops of methyl orange, and titrate with a 0.1 *N* hydrochloric acid solution until a pink colour appears.

3. Calculate the sodium chloride content in grammes in a packet of powder by formula (1.3):

$$X = \frac{VKTb}{a} = \frac{VK \times 0.005845 \times 0.25}{0.1}$$

where *V* is the volume of the 0.1 *N* silver nitrate solution, ml, *T* = 0.005845 g/ml, *a* is the mass of the sample, g, and *b* is the mass of one powder, g.

Calculate the sodium tetraborate content in grammes in a packet of powder by formula (1.3):

$$X = \frac{VK \times 0.01907 \times 0.25}{0.1}$$

where *V* is the volume of the 0.1 *N* hydrochloric acid solution, ml, and *T* = 0.01907 g/ml.

4. Compare the result with the prescription and conclude whether the medicinal preparation may be dispensed.

5. Propose reactions for the identification of sodium tetraborate and sodium chloride. Write their equations.

Chapter 7. Group II Elements

The atoms of Group II elements have two electrons in their outer electron layer that are at a considerable distance from the nucleus. These two electrons are therefore easily detached from the atoms, and the latter transform into positive doubly charged ions.

The difference in the structure of the last but one outer layer in a number of Group II elements explains the existence of two subgroups, namely, the main one (Group IIA) including the alkaline-earth metals (beryllium, magnesium, calcium, strontium, barium, radium), and the secondary one (Group IIB) including the transition elements zinc, cadmium and mercury.

All the elements in Group IIA except for beryllium and radium have very pronounced metallic properties. The alkaline-earth elements (calcium, magnesium, and barium) are light metals and are highly reactive.

The larger the atomic mass, the more electrically positive is the metal. Barium is just as strong a reducing agent as the alkali metals. The oxides of the alkaline-earth metals react with water to form hydroxides whose solubility grows from beryllium hydroxide to barium hydroxide. The basic nature of these compounds increases in the same sequence.

The Group IIB elements (Zn, Cd, Hg), like the Group IIA ones, exhibit an oxidation state of $+2$, but there is also a difference between them due to the different radii of their atoms and different ionization potentials. The metallic properties of Group IIB elements decrease from zinc to mercury. Their hydroxides are insoluble in water and have weakly basic properties.

The elements Mg, Ca, Ba, Zn, and Hg are of interest for medicine. All of them are contained in the most important drugs.

The most toxic of the Group II elements is barium in its soluble compounds, which are employed only as reagents and poisons to combat insects and rodents. Barium sulphate is used in medicine; it is virtually insoluble in any solvent (see Sec. 7.3).

7.1. MAGNESIUM COMPOUNDS

Magnesium is widely found in nature. Having a comparatively high chemical activity, it is not encountered in the free state, but mainly in the form of carbonates, in the widespread minerals dolomite $\text{MgCO}_3 \cdot \text{CaCO}_3$ and magnesite MgCO_3 . Magnesium is also contained in many silicates, for example talc $3\text{MgO} \cdot 4\text{SiO}_2 \cdot \text{H}_2\text{O}$, and its salts are encountered in the soil, in natural water, especially sea water, and in many mineral springs.

The significance of magnesium in the development of life on the Earth is very great. It is contained in the green plant pigment chlorophyll, and thus participates in the process of photosynthesis by plants.

Magnesium compounds play a considerable role in the activity of the central nervous system of living organisms. In its physiological action, magnesium is an antagonist of calcium. Magnesium salts cause narcosis and paralysis, while calcium compounds abolish this effect. Conversely, the action rendered by calcium salts is abolished by magnesium.

Magnesium oxide, burnt magnesia, basic magnesium carbonate, white magnesia, magnesium trisilicate, and magnesium sulphate are pharmacopoeial preparations of magnesium. The first three preparations exhibit an antacid action, i.e. are taken to lower the acidity of the gastric juice. They act in the same way as very mild purgatives. Magnesium sulphate is used as a tranquilizer, spasmolytic, and purgative agent.

Magnesium Sulphate (*Magnesii sulfas*)

$\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$

M.m. 246.50

Magnesium sulphate was first used as a drug in England, where it was produced from the water of mineral springs at Epsom. Unlike other preparations, magnesium sulphate has a bitter salty taste. (It is also called Epsom salts, after its origin.)

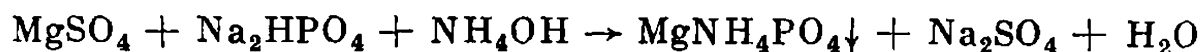
Magnesium sulphate is quite abundant in nature in the form of kieserite $\text{MgSO}_4 \cdot \text{H}_2\text{O}$ ($\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$), which is a constant satellite of rock salt NaCl . A large amount of magnesium sulphate is contained in sea water.

The preparation is obtained from magnesite MgCO_3 by treating it with sulphuric acid:



The solution is concentrated by evaporation up to crystallization, and the product is $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$. It forms colourless prismatic crystals weathering in the air. It dissolves well in water and does not practically dissolve in alcohol.

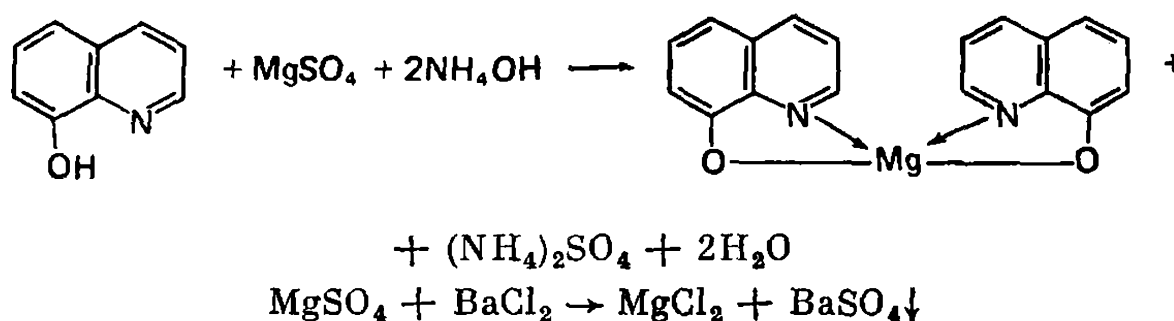
The preparation is identified by reactions for the cation Mg^{2+} and anion SO_4^{2-} . The main reaction for Mg^{2+} recommended by the State Pharmacopoeia is the formation of the double salt ammonium and magnesium phosphate when the preparation is reacted with disodium hydrogen phosphate in the presence of ammonium chloride:



White

If this reaction is conducted on a slide, the magnesium ammonium phosphate crystals (MgNH_4PO_4) rapidly form a crystallohydrate with six molecules of water. Under a microscope, these crystals have a definite shape, which identifies the preparation.

Among organic reagents used to detect the magnesium ion Mg^{2+} , 8-hydroxyquinoline is the most widespread and specific one. When it is added together with an ammonia solution and ammonium chloride NH_4Cl to magnesium compounds, it yields greenish yellow magnesium hydroxyquinolate. The sulphate ion in the preparation is detected by a solution of barium chloride, which produces a white precipitate of barium sulphate:



Since magnesium sulphate is taken orally, and in large doses, the State Pharmacopoeia contains strict requirements to its purity. The most dangerous admixture is arsenic. The content of this impurity must not exceed 0.0002%. The content of other possible admixtures such as chlorides, heavy metals, and moisture is also tolerated within the prescribed limits.

Natural magnesium compounds are sometimes coloured green owing to admixtures of iron compounds, and since these minerals are used to produce magnesium preparations, the latter may also have a slight colour. This is why the State Pharmacopoeia requires that the transparency and colour of a magnesium sulphate solution be determined.

The preparation used for injections (*Solutio Magnesii sulfas* 20% aut 25% pro injectionibus) is tested for the presence of manganese.

The quantitative determination is conducted by the complexometric method.

Magnesium sulphate is widely used in medicine as a purgative. It is taken orally in a dose of 15-30 g.

In the parenteral use of magnesium sulphate, it has a tranquilizing action on the central nervous system. At a concentration of the preparation in the blood of 9-10 mg/litre, a soporific effect occurs, and at 15-18 mg/litre—a narcotic state. Larger concentrations may cause depression of respiration.

Magnesium sulphate is employed:

(1) as a spasmolytic agent in hypertension in the form of a 25% solution (subcutaneously);

(2) as a parturifacient in doses of 10-20 ml of a 25% solution (intramuscularly);

(3) as an anticonvulsive agent in the same doses as in (2);

(4) as a bilogenic agent in the form of a 20-25% solution (orally).

In cases of depression of respiration due to an overdose, a 10% calcium chloride solution is introduced intravenously.

Magnesium sulphate is produced in a powder and in ampoules containing 2.5, 10, and 20 ml of a 25% solution.

7.2. CALCIUM COMPOUNDS

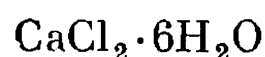
Calcium is one of the most widespread elements in nature. Owing to its high chemical activity, it is found in nature only in the bound state. It occurs in the form of numerous deposits of limestones, chalk, and marble, which are natural varieties of calcium carbonate CaCO_3 . It is also encountered in large amounts in gypsum $\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$, phosphorite $\text{Ca}_3(\text{PO}_4)_2$, and various calcium-containing silicates.

All the natural calcium compounds, especially carbonates, are used as sources for preparing medicinal preparations of calcium, marble being employed the most frequently for this purpose as the purest material free of admixtures. Calcium plays an important role in the vital activities of an organism. It is contained in tooth tissues, bones, nerve tissues, muscles, and blood. Calcium ions promote the vital activities of cells, facilitate the contraction of the skeletal and cardiac muscles, and are needed for the formation of bone tissue and the process of blood coagulation.

A decrease in the calcium ion concentration in the blood increases the stimulation of the muscles, which sometimes results in convulsions. Solutions of calcium salts eliminate the itching caused by an allergic state, therefore they are related to antiallergic drugs.

The calcium compounds used in medicine include calcium oxide (burnt lime), burnt calcium sulphate (burnt gypsum), precipitated calcium carbonate (precipitated chalk), calcium chloride, and salts of organic acids (calcium glycerophosphate, calcium gluconate, etc.). Calcium chloride is a pharmacopoeial preparation.

Calcium Chloride (*Calcii chloridum*)



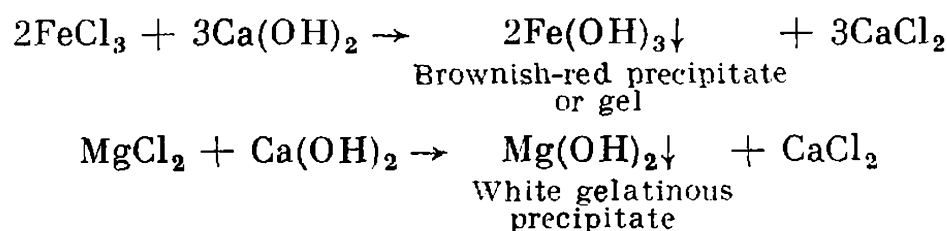
M.m. 219.08

Calcium chloride intended for medicinal purposes is produced by treating calcium carbonate (marble) with hydrochloric acid:



The carbon dioxide volatilizes, and pure calcium chloride $\text{CaCl}_2 \cdot 6\text{H}_2\text{O}$ crystallizes from the water.

Natural calcium carbonate is often accompanied by admixtures of magnesium and iron which when treated with hydrochloric acid transform into the complex salt $\text{MgCl}_2 \cdot \text{FeCl}_2$. To purify the preparation from these salts, the obtained calcium chloride solution is saturated with gaseous chlorine and then treated with calcium hydroxide; the iron(II) chloride FeCl_2 is oxidized to iron(III) chloride FeCl_3 ; and the following reactions occur:

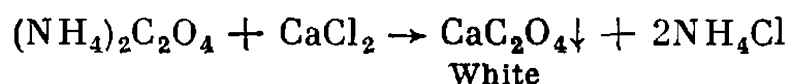


The above reactions reveal that the solution becomes enriched in calcium chloride, while the admixtures precipitate in the form of iron and magnesium hydroxides. The solution is poured off the precipitate and evaporated. The calcium chloride crystallizes in the form of the crystallohydrate $\text{CaCl}_2 \cdot 6\text{H}_2\text{O}$ (calcium chloride hexahydrate).

Pharmacopoeial calcium chloride forms odourless colourless prismatic crystals with a bitter salty taste. It dissolves very readily in water, and this process is attended by great cooling of the solution. It dissolves readily in 95% alcohol. The preparation is very hygroscopic and runs in the air. At 94°C , it melts in its crystallization water. Aqueous solutions have a neutral reaction. When heated to 200°C , it loses part of its crystallization water and transforms into calcium chloride dihydrate $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$, which vigorously absorbs moisture from the air and runs. Calcium chloride dihydrate $\text{CaCl}_2 \times 2\text{H}_2\text{O}$ differs in its appearance from the pharmacopoeial preparation in that it forms porous, very light pieces. It is used to dry gases. When heated to 800°C , it loses its crystallization water completely. Anhydrous calcium chloride is used to dry liquids except for ether and alcohol because it forms complex compounds with them of the type $\text{CaCl}_2 \cdot 3\text{C}_2\text{H}_5\text{OH}$.

Since the preparation is highly hygroscopic and can run in humid air, its composition is not constant. This may result in an inaccurate dosage when preparing drugs containing calcium chloride. With this in view, a 50% solution (*Calcium chloratum solutum* 50%) is prepared at pharmacies, and this concentrate is used to prepare the required drugs.

The preparation is identified by reactions for the cation Ca^{2+} and the anion Cl^- . A very sensitive reaction for Ca^{2+} is that with ammonium oxalate, which is an official one:



The precipitate is soluble in mineral acids and is insoluble in acetic acid.

In addition to the official reaction, other reactions can be used to identify calcium chloride. An example is the formation of a white precipitate when the preparation is reacted with sulphuric acid or alkali metal sulphates:

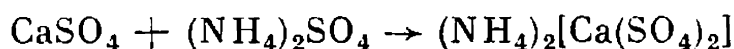


White



White

The calcium sulphate precipitate dissolves in ammonium sulphate with the formation of a colourless complex:



Calcium salts impart a brick red colour to the flame of a burner. No admixtures of soluble salts of barium, iron, aluminium, and of phosphates are tolerated in the preparation. Other possible impurities such as sulphates, heavy metals, arsenic, and magnesium salts are tolerated within the limits established by the relevant standards.

The content of the substance in the preparation is determined by complexometric titration using the indicator Acid Chrome Dark Blue (State Pharmacopoeia). The indicator reacts with Ca^{2+} in an alkaline medium with the formation of a red-violet complex. In titration with Na-EDTA, the colour of the solution at the equivalence point changes to bluish lilac. The content of pure calcium chloride in the preparation must be at least 98.0%.

The literature also describes other methods for the quantitative determination of calcium chloride, namely, the photometric, fluorometric, and gravimetric (oxalate) methods.

Calcium chloride is used very widely in medicine:

(1) as a haemostatic in pulmonary, gastric, nasal, and uterine haemorrhages;

(2) in surgery to improve the coagulation of blood;

(3) in allergic diseases (bronchial asthma, urticaria) for eliminating the itching;

(4) as an antidote in poisoning by magnesium salts.

The preparation is administered orally in the form of a 5-10% solution, or intravenously in a dose of 5-10 ml of a 10% solution. It is dispensed in ampoules containing 5 or 10 ml of a 10% solution, and also in small well sealed glass jars with a stopper sealed with wax. Similar jars should be used to store the preparation in dry premises. Calcium chloride solutions must never be introduced subcutaneously or intramuscularly because this may result in necrosis.

7.3. BARIUM COMPOUNDS

Barium occurs in nature chiefly in the form of sulphates and carbonates, forming the minerals barite BaSO_4 and witherite BaCO_3 . Barium is among the very active elements, it rapidly oxidizes in the air, vigorously reacts with water, and enters into reactions with many elements.

Of the barium salts, only barium sulphate is used in medicine. It is virtually insoluble in water, acids, alkalies, and organic solvents, and is therefore not poisonous.

All the soluble barium salts (chlorides, bromides, iodides, nitrates, cyanides) are very toxic, and this is why they are not employed in medicine. The barium salts that are insoluble in water, but soluble in hydrochloric acid (BaCO_3 , BaS) are also toxic because when they get into the acidic medium of the gastric juice, they transform into the soluble salt barium chloride (BaCl_2).

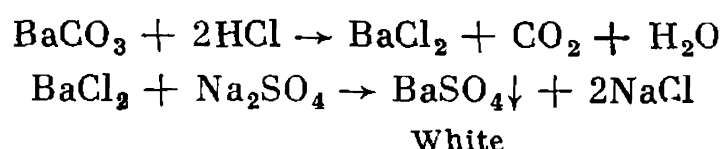
The use of barium sulphate in medicine is based on its impermeability to X rays, which is employed in roentgenology for obtaining contrast X-ray photographs and in the radiosopic investigation of the alimentary tract. It is taken in doses of 50.0-100.0 g in a mixture with water (a "barium meal"). This substance fills the stomach and is opaque to X rays. After a definite time, the substance is completely excreted from the organism. Barium sulphate is a pharmacopoeial preparation.

Barium Sulphate for Radioscopy (*Barii sulfas pro roentgeno*)

BaSO_4

M.m. 233.43

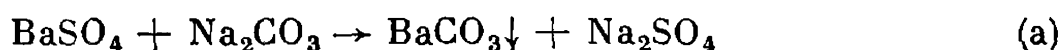
To produce barium sulphate for radioscopy, natural barium carbonate (witherite) is used. It is treated with hydrochloric acid to yield soluble barium chloride BaCl_2 . Sodium or magnesium sulphate is added to the solution of this salt, and a barium sulphate precipitate forms immediately:



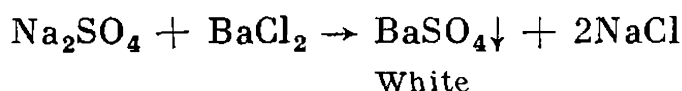
To obtain finely dispersed barium sulphate, a linseed or some other mucous concoction is added to the barium chloride and sodium sulphate solutions. It plays the role of a protective colloid when the barium sulphate forms. The barium sulphate precipitate is thoroughly rinsed to remove impurities, especially chloride ions. If Cl^- is detected in the effluent, it can be presumed that the preparation contains

an admixture of soluble barium chloride. The preparation is also rinsed to remove the ion SO_4^{2-} .

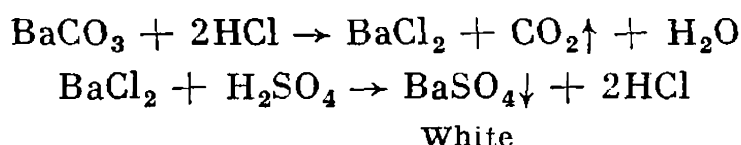
Barium sulphate is a white friable heavy powder without an odour or taste. It cannot be identified directly because it is insoluble. This is why barium sulphate is first transformed into soluble compounds that dissociate with the formation of the ions Ba^{2+} and SO_4^{2-} . For this purpose, the preparation is heated with sodium carbonate:



The precipitate is filtered off, and SO_4^{2-} is determined in the filtrate by adding barium chloride, which produces a white precipitate of barium sulphate:



The barium carbonate precipitate of reaction (a) is treated with hydrochloric acid to transfer it into a soluble salt (barium chloride) in which the Ba^{2+} ion is easily identified by precipitating it with sulphuric acid:



These reactions are official ones.

Volatile barium salts (BaCl_2) colour a burner flame yellow-green.

Barium sulphate is taken orally in large doses (50-100 g), therefore the State Pharmacopoeia contains strict requirements to the purity of the preparation. It must contain no admixtures of barium salts soluble in water (BaCl_2) or in acids (BaCO_3 , BaS).

No admixtures of sulphites and arsenic are tolerated in the preparation. Arsenic may get into it if sulphuric acid, which may contain admixtures of arsenic, was used to produce it instead of sodium or magnesium sulphate. The State Pharmacopoeia tolerates admixtures of chlorides, sulphates, and heavy metals in the preparation within the prescribed limits.

To detect possible impurities, several extracts are made from the preparation:

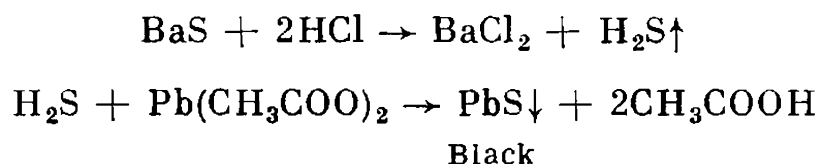
(1) it is treated with acetic acid and tested for soluble barium salts and barium carbonate (no precipitate should appear during one hour when sulphuric acid is added);

(2) it is treated with hydrochloric acid, and barium sulphide, iron, and salts of other heavy metals are detected;

(3) an aqueous extract must be neutral and contain only traces of chlorides and sulphates;

(4) the preparation is treated with nitric acid, and barium and calcium phosphates are identified using ammonium molybdate.

The preparation should be tested especially thoroughly for barium carbonate and sulphide. If admixtures of sulphides are present, the extract obtained when treating the preparation with hydrochloric acid will have an odour of hydrogen sulphide. But in this case an organoleptic test is not sufficient, therefore the extract of the preparation is placed into a test tube, covered with filter paper wetted with a lead acetate solution, and heated. If an impurity of barium sulphide BaS is present, the evolving hydrogen sulphide will react with the lead acetate and the paper will darken owing to the formation of lead sulphide PbS:



The State Pharmacopoeia requires that the degree of dispersion of the preparation be determined.

The quantitative determination of the preparation is not required. Barium sulphate is supplied to pharmacies in the factory packing, i.e. in well glued double paper packages (the inner package must be of oil-paper). The preparation is not done up at pharmacies. The label must contain the full name of the preparation in the native language and in Latin. The series, date of production, who controlled the quality and when must also be indicated. The preparation must be kept in well closed jars or packages away from potassium and sodium carbonates.

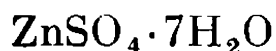
7.4. ZINC COMPOUNDS

Zinc is found in nature in the form of the minerals smithsonite (or calamine) ZnCO_3 and zinc blende (or sphalerite) ZnS . Zinc has been found in the muscular, dental, and nerve tissues of a human organism. The use of zinc compounds in medicine is based on the fact that zinc, like some other heavy metals, forms compounds with proteins—albuminates, and the soluble albuminates can have an effect ranging from a weak astringent to a sharply cauterizing one. Insoluble albuminates generally form a film on a tissue surface and thus promote the healing of the injury (a drying action).

Zinc compounds are toxic in large doses. They may be employed locally as astringent and cauterizing agents. When taken orally, zinc compounds cause vomiting.

The pharmacopoeial preparations of zinc include zinc oxide and zinc sulphate.

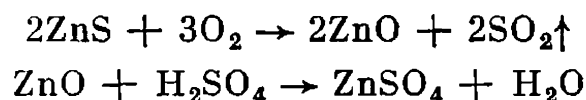
Zinc Sulphate (*Zinci sulfas*)



M.m. 287.54

Zinc sulphate was used in medicine from time galore under the name of white vitriol to distinguish it from the coloured copper and iron vitriols.

Zinc sulphate is produced from its ore—zinc blende ZnS . The latter is subjected to roasting. The zinc sulphide transforms into the oxide, which is then treated with dilute sulphuric acid, and zinc sulphate forms in the solution:



The impurities contained in the raw material (copper, cadmium, lead) do not dissolve. To remove admixtures of iron, the solution is treated with hydrogen peroxide:

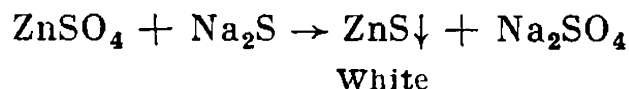


The formed iron(III) sulphate is reacted with zinc oxide in the presence of water, the formed iron(III) hydroxide precipitate is filtered off, and the solution containing the zinc sulphate is evaporated until the salt crystallizes in the form of the heptahydrate ($\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$).

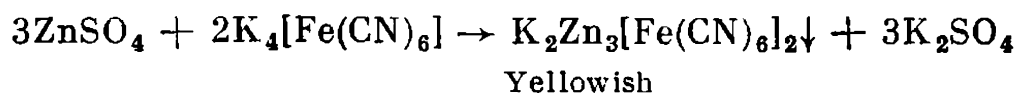
Zinc sulphate forms colourless transparent crystals or a finely crystalline powder with an astringent taste and without an odour. It dissolves very readily in water, slowly in glycerin, and is insoluble in alcohol. It weathers in the air.

The preparation is identified by the reactions indicated for zinc oxide. The sulphate ion is determined by the formation of a white precipitate.

A typical reaction for Zn^{2+} is the reaction with a solution of sodium sulphide, which in an acidic medium precipitates white zinc sulphide ZnS from zinc salts (a distinction from other salts of heavy metals):

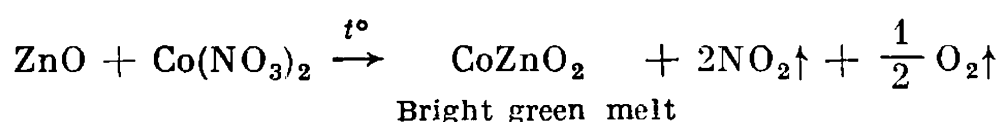


Another reaction confirming Zn^{2+} in the preparation is the reaction with a solution of potassium ferrocyanide. A yellowish crystalline precipitate of a double salt forms that is insoluble in acids, but dissolves in alkalis:



These two reactions are official ones.

A specific reaction for zinc in all its compounds is that of the formation of Rinmann's green. Zinc oxide is roasted with cobalt nitrate, and a characteristic green colour is obtained—Rinmann's green:



The quality of the preparation is considered to be proper if it contains no admixtures of iron, copper, aluminium, magnesium, calcium, and other heavy metals. All these impurities are detected by known analytical reactions. An admixture of arsenic in the preparation of not over 0.0001% is tolerated.

The content of the substance in the preparation is determined by the complexometric method in the presence of an ammonia buffer solution and the indicator Acid Chrome Black Special.

Zinc sulphate is used externally as an antiseptic and astringent agent in ophthalmology in the form of 0.1, 0.25, and 0.5% solutions. Zinc sulphate is often prescribed together with boric acid in eye drops. It is employed in gynaecology for irrigation in the form of a 0.1-0.5% solution. It is rarely prescribed for oral administration as an emetic.

It is dispensed in the form of a powder. It must be stored with care in well closed jars. It is listed in Group B.

Zinc Oxide (*Zinci oxydum*)

ZnO

M.m. 81.38

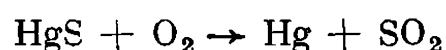
Zinc oxide is a white amorphous powder with a yellowish tint that readily absorbs carbon dioxide from the air. A characteristic property of zinc oxide is that it turns yellow when roasted, and when cooled—white.

Zinc oxide is used externally in the form of dusts or ointments as an astringent, drying, and disinfecting agent in skin diseases.

7.5. MERCURY COMPOUNDS

Mercury is a liquid metal whose lustre resembles that of silver. This is why the Greeks called it "silver water" (it was also called quicksilver).

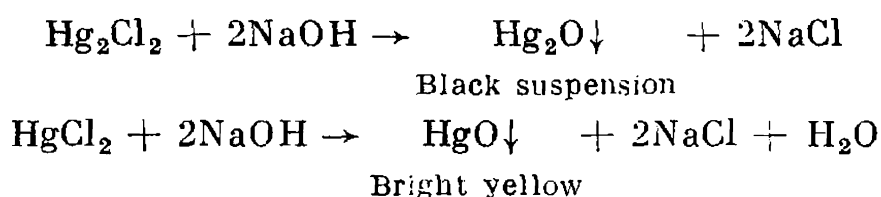
It is not abundant in nature. It is sometimes encountered in the free state interspersed in rock, but it occurs chiefly in the form of mercury sulphide HgS (cinnabar) of a bright red colour. Cinnabar is the main source of mercury. To produce the latter, the cinnabar is roasted in special furnaces in a stream of air at 360 °C:



Mercury is the only metal that is in the liquid state at room temperature. The liquid evaporates slowly. Its specific gravity is 13.6. At -39°C it freezes and transforms into a solid white mass. At 357°C it boils. Its vapour is very poisonous.

Among the chemical properties of mercury, of interest is its ability to dissolve many metals and form liquid and solid alloys called **amalgams**. Iron and nickel do not dissolve in mercury and do not form amalgams with it, therefore mercury may be stored and transported only in iron or nickel vessels. Sodium amalgam is used in laboratory practice as a reducing agent. Tin and silver amalgams solidify well as soon as they are prepared and are used in stomatology for filling teeth.

Mercury forms no hydroxides—this is a feature of it. When an alkali is reacted with a mercury salt, anhydrous oxides form:



Being in group IIA, mercury differs from its analogues (zinc and cadmium) in that it forms two kinds of salts, i.e. mercury(I) salts (HgNO_3 , Hg_2Cl_2 , etc.) and mercury(II) salts (HgCl_2 , $\text{Hg}(\text{NO}_3)_2$, and $\text{Hg} \begin{smallmatrix} \nearrow \text{NH}_2 \\ \searrow \text{Cl} \end{smallmatrix}$).

The pharmacopoeial preparations include mercury(II) compounds, namely, yellow mercury oxide, mercury dichloride, mercury amido-chloride, mercury(II) oxycyanide, and mercury(II) cyanide.

The inorganic preparations of mercury are used as antiseptics, diuretics, and purgatives. The antiseptic action of mercury compounds is based on the ability of the mercury ion to precipitate proteins.

The diuretic effect of some mercury salts consists in that when excreted via the kidneys, they irritate the kidney epithelium and facilitate urination. Similarly, mercury compounds excreted via the intestine and irritating it have a purgative action.

Soluble mercury salts are very poisonous and relate to Group A.

Mercury Dichloride or Corrosive Sublimate (*Hydrargyri dichloridum*)

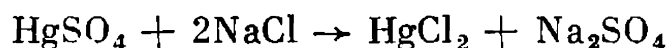
HgCl_2

M.m. 271.50

Mercury dichloride can be produced in various ways:

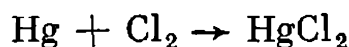
(1) by dissolving metallic mercury in sulphuric acid with the following evaporation of the obtained solution of mercury sulphate

HgSO₄ with sodium chloride:



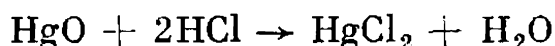
When the mixture is heated, the mercury dichloride sublimes, while the sodium sulphate remains in the form of the dry salt;

(2) by reacting metallic mercury with chlorine at 335-340 °C:



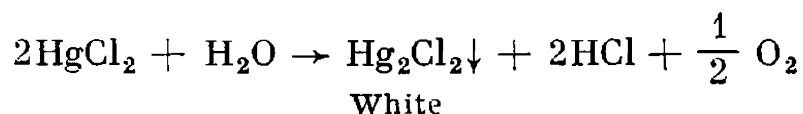
To purify the mercury dichloride from mercury monochloride, it is sublimed and then crystallized from alcohol or water in which mercury monochloride is insoluble;

(3) by dissolving mercury oxide in hydrochloric acid:



In the pure form, mercury dichloride is a white heavy powder or radial crystals melting at 265 °C and evaporating at 295 °C. The preparation is soluble in ether, and well soluble in boiling water and alcohol. An aqueous solution of mercury dichloride has an acid reaction to litmus.

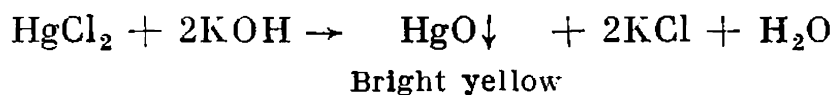
Dry mercury dichloride is more stable than its aqueous solutions. When the latter are stored for a long time in the light, a white precipitate of mercury monochloride forms together with hydrochloric acid and oxygen:



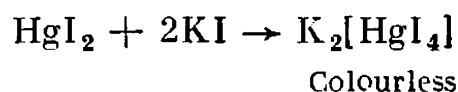
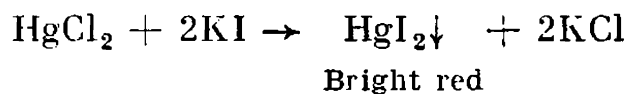
Mercury dichloride forms insoluble compounds with proteins and alkaloids.

The preparation is identified by the reactions for the cation Hg²⁺ and the anion Cl⁻. The State Pharmacopoeia recommends the following reactions for Hg²⁺:

(a) a reaction with alkali solutions; when an alkali solution is reacted with a solution of mercury(II) salts, a yellow precipitate of mercury(II) oxide forms:

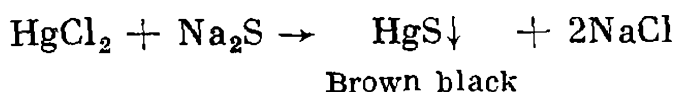


(b) a reaction with a potassium iodide solution; when a solution of mercury dichloride is reacted with a potassium iodide solution, a bright red precipitate of mercury diiodide forms that dissolves completely in an excess of potassium iodide:



A solution of this complex salt in a concentrated potassium hydroxide solution is known as Nessler's reagent and is employed as a very sensitive reagent for NH_4^+ ;

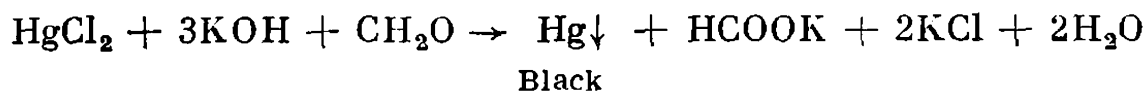
(c) a reaction with a sodium sulphide solution; when the latter is added to a solution of a mercury(II) salt, a brown black precipitate forms that is not soluble in dilute nitric acid:



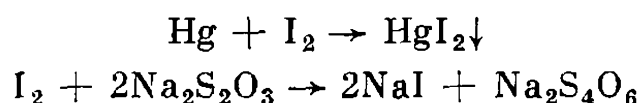
Of these three reactions for a mercury(II) salt, the State Pharmacopoeia recommends that with potassium iodide to identify mercury dichloride.

The quality of mercury dichloride is considered to be proper if its colour is white, it completely evaporates when heated, leaving no residue, and dissolves in water and alcohol.

A number of methods can be used for the quantitative determination of mercury dichloride. The State Pharmacopoeia recommends the reduction of mercury dichloride to free mercury, which is then determined iodimetrically. A solution of formaldehyde in an alkaline medium is used as the reducing agent:



After reduction, the mixture is acidified with acetic acid to neutralize the excess alkali (the latter can react with the iodine) and a standard solution of iodine is added. The mercury dissolves and forms mercury(II) iodide, HgI_2 , while the excess iodine is titrated with sodium thiosulphate:



Mercury dichloride is very poisonous therefore it is not taken orally. Having a disinfecting action, it selectively destroys microorganisms by decomposing their proteins. Mercury dichloride solutions (1:1000 and 2:1000) are used to disinfect linen, clothing, for washing walls, objects used in caring for patients, etc.

Mercury dichloride solutions should be protected from the effect of light, which facilitates their decomposition. To prevent the decomposition of the mercury dichloride and ensure its better dissolution, sodium or ammonium chloride is added to the solution (a soluble complex forms).

Mercury dichloride solutions are generally coloured red or blue to distinguish them from other solutions. Bottles with mercury dichloride solutions must bear labels warning that the contents are poisonous. Mercury dichloride is usually dispensed in tablets contain-

ing equal parts of it and sodium chloride (0.5 or 1.0 mg each). These tablets are customarily coloured pink with eosine.

Mercury dichloride produces precipitates with alkaloids and proteins. Moreover, many organic compounds such as sugar and arabic gum reduce mercury dichloride. All this must be taken into consideration when formulating a prescription with mercury dichloride.

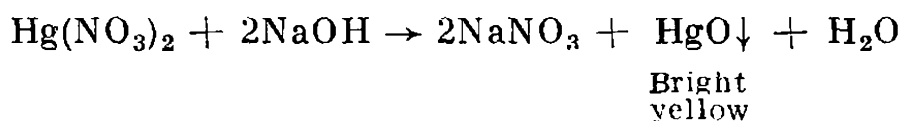
Mercury dichloride (corrosive sublimate) is a strong poison. Store it in a locked cupboard in a dark place. The highest single and daily dose is 0.02 g. It belongs to Group A.

Yellow Mercury Oxide (*Hydrargyri oxydum flavum*)

HgO

M.m. 216.59

To prepare yellow mercury oxide, the reactions of its precipitation from soluble mercury salts are used. Mercury dichloride or dinitrate is used most frequently for this purpose. A concentrated solution of the mercury(II) salt is slowly poured into a dilute alkali solution:



After settling of the mercury oxide precipitate, the liquid is poured off, the precipitate is washed by decantation until it is no longer alkaline, and is dried. All the operations must be performed in the dark, otherwise the black mercury(I) oxide Hg_2O can form.

Yellow mercury oxide is a heavy finely dispersed yellow or orange-yellow powder. It is insoluble in water, but readily dissolves in hydrochloric, nitric, and acetic acids. It gradually darkens in the light.

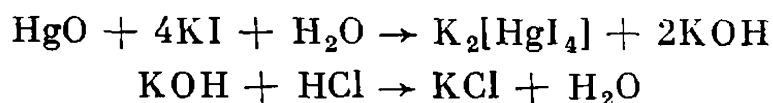
The preparation is identified by reactions for Hg^{2+} . For this purpose, it is treated with dilute hydrochloric acid to obtain a soluble salt of mercury(II) in which the cation Hg^{2+} is determined by the relevant reactions described for mercury dichloride:



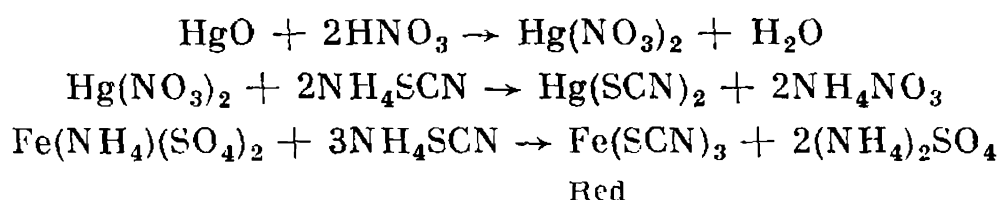
The preparation must be free of admixtures of alkalies, mercury(I) salts, and metallic mercury.

The content of the preparation can be determined by two methods, namely, neutralization and the thiocyanide (rhodanide) one. The former is the official method.

The preparation is determined by neutralization indirectly by reaction with potassium iodide. When a potassium iodide solution is reacted with yellow mercury oxide, the products are a soluble complex salt and an alkali. The latter is titrated with an acid using methyl orange as the indicator:



The thiocyanide method consists in dissolving the oxide in nitric acid and then titrating the obtained salt with ammonium thiocyanide in the presence of ammonium iron alum:



Yellow mercury oxide is used as a mild antiseptic for preparing eye ointments.

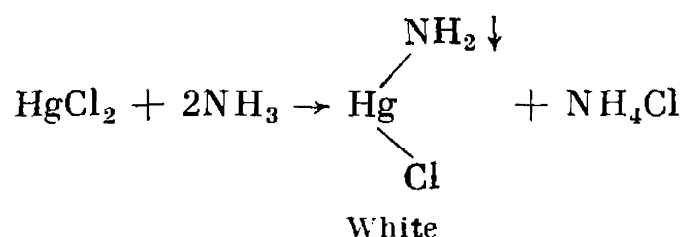
It should be stored with care in well closed dark glass jars because the action of light may cause mercury(I) oxide to form. This is detected by darkening of the preparation. It is listed in Group B.

Mercury Amidochloride (*Hydrargyri amidochloridum*)

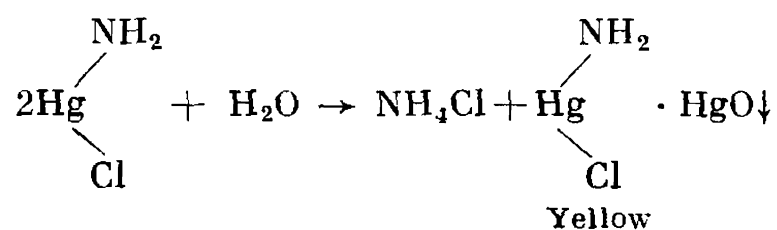
HgNH_2Cl

M.m. 252.07

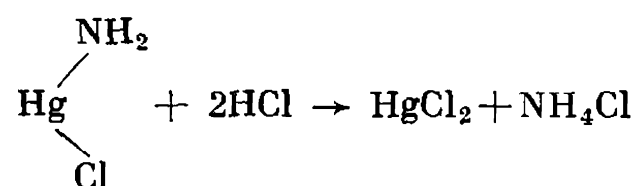
Mercury amidochloride is usually prepared by reacting mercury dichloride with an ammonia solution:



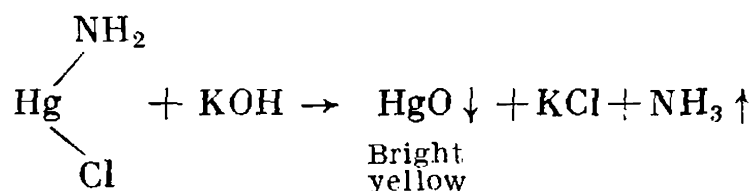
The mercury amidochloride precipitate is filtered off, washed with water to remove the ammonium chloride, and dried in a drying cabinet at a temperature not exceeding 50 °C. A small amount of water should be used for washing, because owing to hydrolysis of the product the basic salt can form and the preparation turns yellow:



Mercury amidochloride is a snow-white amorphous powder (or lumps). It is insoluble in water, alcohol, and ether. It dissolves when heated in dilute hydrochloric, nitric, and acetic acids:



When mercury amidochloride is heated with an alkali, yellow mercury oxide precipitates, and a smell of ammonia is felt:



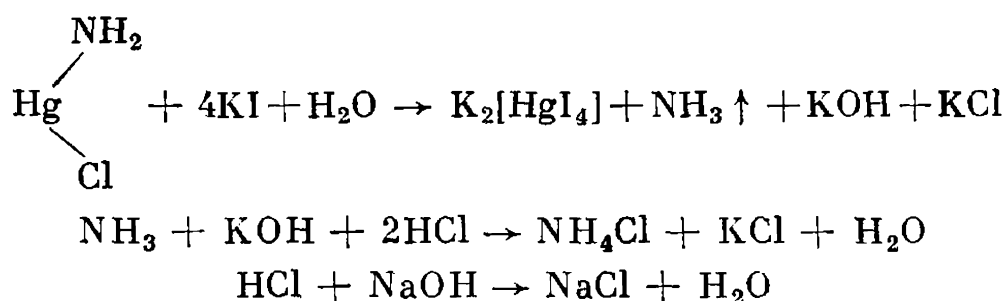
After separation of the mercury oxide precipitate, the chloride ion is detected in the filtrate by the action of a silver nitrate solution.

After being dissolved in acids (hydrochloric, nitric, acetic), mercury amidochloride gives all the reactions characteristic of mercury(II) compounds.

The preparation must contain no admixtures of carbonates and mercury(I) compounds. The absence of the former is established by the complete dissolution of the preparation in hydrochloric acid without the evolution of carbon dioxide.

The preparation is determined quantitatively by neutralization. In this method, an aqueous solution of potassium iodide is reacted with mercury amidochloride. Potassium hydroxide and ammonia form in an amount equivalent to the mercury amidochloride; they are titrated with an acid using a methyl red indicator.

To avoid losses of ammonia owing to its possible evaporation, an excess of a titrated hydrochloric acid solution is added beforehand, and it binds the alkali and ammonia, while the excess of acid is titrated with an alkali:



When mercury amidochloride is triturated in a mortar with iodine, it ignites after a certain time owing to the formation of nitrogen iodide NI_3 .

Similar decomposition can also occur if the mixture is wetted with water or alcohol. With this in view, mercury amidochloride must never be prescribed with iodine and moreover with a tincture of iodine.

Mercury amidochloride is poisonous and is not taken orally. It is used in 3-10% ointments in various skin diseases. It is also used in cosmetic ointments.

It should be stored with care (Group B) in well closed orange glass bottles.

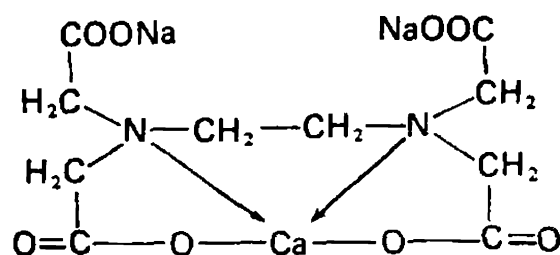
7.6. MERCURY ANTIDOTES

Soluble mercury salts are very poisonous. The first signs of mercury poisoning are a sharp metallic taste in the [mouth, pains in the stomach, vomiting, loose bowels (diarrhoea), and cardiac depression.

Persons suffering from kidney ailments are especially sensitive to mercury preparations.

First aid in mercury poisoning consists in taking of a metal antidote (*Antidotum metallorum*) or a suspension of activated carbon. One must simultaneously take albumin water, milk, mucilagenous decoctions, or burnt magnesia with water. Sodium chloride and food products containing it must never be used because this can enhance the poisoning owing to the formation of the soluble and very poisonous mercury dichloride.

Another antidote used in poisoning by mercury salts is sodium calcium edetate, also known as tetacin calcium. It is a white crystalline powder. In its chemical structure, tetacin calcium is a cyclic compound in which the calcium can be substituted by ions of heavy metals with the formation of water-soluble complexes with a low toxicity. The complexes are rapidly excreted with the urine, which underlies the use of this preparation as an antidote in poisoning by heavy metal salts:



Tetacin calcium

A 10% solution of tetacin calcium for injections is a pharmacopoeial preparation

REVIEW QUESTIONS

1. Explain why the Group II elements readily donate electrons and transform into positively charged ions.
2. Explain the existence of two subgroups in Group II.
3. What characterizes the hydroxides of the group IIA elements and those of the group IIB ones?
4. Why does magnesium sulphate dissolve well in water and why can it weather?
5. What are the requirements to the storage of calcium chloride and what is this due to?
6. Why is barium sulphate fused with sodium carbonate before conducting identification reactions? Write the equations of the reactions.

7. Why must the purity of barium sulphate meet increased requirements?
8. Why is the presence of soluble barium salts in a barium sulphate preparation especially dangerous?
9. What are the requirements to the storage of barium sulphate?
10. Why does zinc oxide fail to dissolve in water?
11. What explains the solubility of a zinc oxide preparation in acids and alkalies?
12. What reaction of the medium do aqueous solutions of mercury dichloride have?
13. Why is it not allowed to keep aqueous mercury dichloride solutions in the light for a long time?
14. Why is it important for a pharmacist to know and remember that mercury dichloride forms precipitates with proteins and alkaloids?
15. What properties of mercury dichloride are used for the quantitative determination of the preparation?
16. How is mercury dichloride stored and why?
17. Can the chloride ion be detected in mercury amidochloride in an aqueous solution by a conventional analytical procedure?
18. Why must yellow mercury oxide and mercury amidochloride not be taken orally?

PRACTICAL LESSON

Analysis of a 10% Calcium Chloride Solution

1. Write the prescription in Latin.
2. Perform identification reactions:
 - (a) add two drops of an ammonium oxalate solution to 1 ml of the analyte solution. A white precipitate forms that is soluble in hydrochloric acid and insoluble in acetic acid;
 - (b) add one drop of a 2% silver nitrate solution to 1 ml of the analyte solution. A white precipitate forms that is soluble in an ammonium hydroxide solution.

Write the equations of the chemical reactions.
3. Carry out a quantitative determination:
 - (a) by the complexometric method.
Put 2 ml of the analyte solution into a 100-ml measuring flask, add water up to the mark, thoroughly stir the contents, transfer 5 ml of the dilute solution into a titration flask, add 2 ml of an ammonia buffer, two drops of the indicator Acid Chrome Dark Blue, and titrate with a 0.05 *M* solution of Na-EDTA until the colour of the indicator changes;
 - (b) by the refractometric method.

Compare the result obtained with the preceding one. Arrive at a conclusion on the merits and shortcomings of the two methods. Write the equations of the chemical reactions.
4. Calculate the content of calcium chloride in per cent in the solution by formula (1.2):

$$X = \frac{VKTV_1}{aV_2} \times 100 = \frac{VK \times 0.01095 \times 100}{2.0 \times 5.0} \times 100$$

where *V* is the volume of a 0.05 *M* solution of Na-EDTA, ml, *T* = 0.01095 g/ml, and *a* is the volume of the preparation taken for the determination, ml.

5. Conclude whether this solution is indeed calcium chloride, whether its content corresponds to the prescription, and whether it may be dispensed.
6. Propose other possible methods for the quantitative determination of calcium chloride. Write the equations of the reactions.

Analysis of a 10% Magnesium Sulphate Solution

1. Write the prescription in Latin.
2. Perform identification reactions according to the State Pharmacopoeia. Write the equations of the chemical reactions.
3. Carry out a quantitative determination (the refractometric method).
4. Arrive at a conclusion on the qualitative and quantitative correspondence of the analyte solution to the prescription.
5. Can magnesium sulphate be determined quantitatively by another method? Give a chemical substantiation.

Analysis of a 0.25% Zinc Sulphate Solution

1. Write the prescription in Latin.
2. Perform identification reactions (the analyte solution should give characteristic reactions for zinc and sulphate ions).
 - (a) add a few drops of a sodium sulphide solution to several drops of the analyte solution. A white precipitate forms that readily dissolves in dilute hydrochloric acid and does not dissolve in acetic acid;
 - (b) a white gelatinous precipitate insoluble in dilute hydrochloric acid forms with a potassium ferrocyanide solution;
 - (c) add a few drops of a barium chloride solution to a few drops of the analyte solution. A white precipitate forms that is insoluble in organic solvents. Write the equations of the chemical reactions.
3. Carry out a quantitative determination (the complexometric method). Put 2 ml of the analyte solution into a conical titration flask, add 5 ml of an ammonia buffer, three drops of Acid Chrome Dark Blue, and titrate with a 0.05 *M* Na-EDTA solution until the colour turns blue.
4. Calculate the content of zinc sulphate in per cent in the solution by formula (1.1):

$$X = \frac{VKT}{a} \times 100 = \frac{VK \times 0.01438}{2.0} \times 100$$

where *V* is the volume of the 0.05 *M* solution of Na-EDTA, ml, *T* = 0.01438 g/ml, and *a* is the volume of the preparation taken for titration, ml.

5. Conclude whether a zinc sulphate solution has been submitted for analysis, whether its content corresponds to what is indicated in the prescription, and whether it may be dispensed.
6. Can zinc sulphate be determined quantitatively by other methods? Write the equations of the reactions.

Analysis of Barium Sulphate

Divide the powder to be analysed into six portions (one of them is for reference).

1. Add 5 ml of water to a part of the powder, boil, cool, filter off the solid matter, and in the filtrate test:
 - (a) the reaction of the medium with indicator paper;
 - (b) for chlorides (if present, the addition of a silver nitrate solution will produce a white suspension soluble in an ammonium hydroxide solution);
 - (c) for sulphates (if present, a white precipitate insoluble in organic solvents will form when a barium chloride solution is added); give attention to the solubility of this precipitate in hydrochloric acid.
2. Add 2 ml of acetic acid and 3 ml of water to a new portion of the powder, filter off the solid matter, and determine the presence of salts of heavy

metals in the filtrate (if present, a black precipitate will form with a sodium sulphide solution).

3. Add 1 ml of hydrochloric acid to a portion of the powder (should carbonates be present, bubbles of a gas evolve), next add 3 ml of water, heat, cool, and in the filtrate obtained after filtering off the solid matter, test:

(a) for iron(II) salts (if present, a blue colour forms with a solution of potassium hexacyanoferrate(III));

(b) for barium salts (if present, a white precipitate insoluble in organic solvents forms when a sulphuric acid solution is added).

4. Add 3 ml of nitric acid to a portion of the powder, heat, cool, filter off the solid matter, and determine whether the filtrate contains phosphates (if present, a white precipitate forms when a magnesia mixture is added).

5. Add 2 ml of water, 1 ml of sulphuric acid, and two drops of a potassium permanganate solution to a new portion of the powder. The colour should not disappear during 10 minutes (reducing substances).

6. When drawing up your report, indicate what ions contaminate the preparation, write the equations of the reactions, and arrive at a conclusion on the quality of the preparation.

7. Why must the purity of barium sulphate meet increased requirements?

Chapter 8. Group I Elements

All the elements forming Group I have only one electron in their outermost electron layer, which they readily donate and transform into singly charged positive ions with a configuration of the relevant inert gas (the lithium ion acquires the structure of a helium atom, the sodium ion, that of a neon atom, etc.). This explains their very high reactivity relative to electronegative elements such as the halogens.

However, the next-to-last layer of the Group I elements is not the same. This underlies the difference in their properties and the need to divide these elements into two subgroups, namely, IA (representative elements) and IB (transition elements). Group IA includes lithium, sodium, potassium, rubidium, cesium, and francium. All of them have eight electrons in their next-to-last layer. Group IB includes copper, silver, and gold. The next-to-last electron layer of these elements consists of 18 electrons. Some of the electrons of this layer can pass over into the outermost layer and participate in chemical reactions. This explains the varying oxidation state of the Group IB elements.

The Group IA elements are called **alkali metals** because their oxides react with water to form strong alkalies. The alkali metals have sharply pronounced metallic properties because they can readily donate their outermost electrons. A very characteristic feature of the alkali metals is the easiness with which their atoms are excited to emit light. When an alkali metal compound is introduced into the flame of a burner, the flame acquires the colour typical of the given metal. Salts of the alkali metals are used in medicine.

The greatest use has been found in medicine by sodium salts, of which sodium chloride has been described when dealing with the preparations containing halogens (see p. 65).

As regards their action on an organism, the alkali metal salts can be divided into two groups: alkaline salts, for example, carbonates, exhibiting an antacid effect, i.e. neutralizing excess acidity (sodium hydrogen carbonate NaHCO_3 is a pharmacopoeial preparation), and neutral salts (sulphates, halides, and phosphates).

8.1. COPPER AND SILVER COMPOUNDS

The Group IB elements, i.e. copper, silver, and gold, are similar to their Group IA counterparts in that they have an oxidation state of $+1$ in some of their compounds. But copper in most compounds has an oxidation state of $+2$.

Another feature of the Group IB elements distinguishing them from the Group IA alkali metals is their ability to form complexes (especially copper) and to be reduced from their compounds to the free metal (silver is reduced more readily than copper).

Of the inorganic copper compounds, copper sulphate is employed in medicine. It is prescribed orally as an emetic, and externally in catarrhs of the mucous membranes and ulcers owing to its astringent, irritating, and cauterizing action.

Silver belongs to the "noble" metals. In nature, it is chiefly found in the form of compounds with sulphur (Ag_2S). Silver sulphide does not practically occur in the pure form, and is most frequently found in a mixture with the sulphides of other heavy metals, especially lead, copper, and bismuth. And since silver preparations are obtained from natural minerals, they must be tested for the presence of these impurities.

The use of silver preparations in medicine is based on its bactericidal properties. This property of silver was used back in ancient Egypt, where wounds were healed by placing silver plates on them. Water stored for a certain period in silver vessels can remain fresh for a long time. A sterilizing effect is rendered even by the very low concentration of the Ag^+ ion appearing in water when it comes in contact with the metal.

Research has proved that silver ions kill Gram-positive and Gram-negative microorganisms, and also viruses. In the USSR, Academician A. Kulsky developed an electrolytic method for the preparation of silver water (the enrichment of water with silver by electrolysis).

Silver preparations are used in medicine orally and externally as astringent, antiseptic, and cauterizing agents when treating skin, urological, and eye diseases. Silver nitrate (AgNO_3) has found the greatest use among the silver compounds as a good astringent and cauterizing agent. Colloidal preparations where the silver is bound

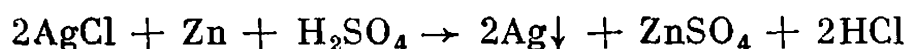
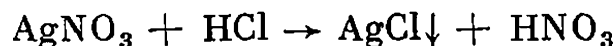
to a protein and is only partly ionized are also employed in medicine. In these preparations, only the disinfecting properties of silver are retained, while its cauterizing effect is lost.

All the soluble compounds of copper and silver are poisonous.

Silver Nitrate (*Argenti nitras*)

AgNO_3 M.m. 169.87

Silver nitrate is prepared by dissolving a copper-silver alloy in nitric acid with heating. To purify the silver nitrate from admixtures, it is precipitated with hydrochloric acid in the form of silver chloride. The latter is reduced with zinc, and the silver freed of impurities is again dissolved in nitric acid:



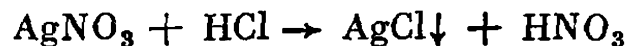
Black



The silver nitrate is treated with a small amount of water, and when left standing crystals form. The crystals are filtered off, rinsed with water, and dried in the dark.

Silver nitrate is composed of colourless transparent crystals in the form of plates or cylindrical rods having a radiant crystalline structure in a fracture. It dissolves readily in water and sparingly in alcohol. The crystals darken in the light.

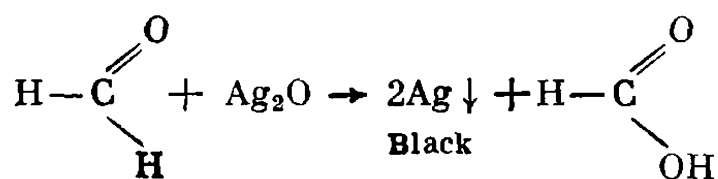
The preparation is identified by a reaction for the ion Ag^+ . When hydrochloric acid or its salts are added to the preparation, a white silver chloride precipitate separates that is insoluble in nitric acid and well soluble in an ammonia solution:



White

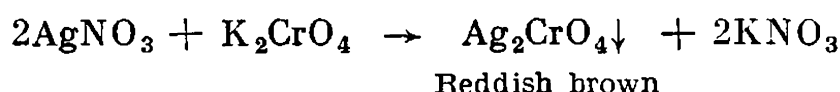


To confirm silver in its salts, their reduction to free silver is employed (the reaction of silver mirror formation). A formaldehyde solution is added to an ammonia solution of silver oxide, and the liquid is heated. After some time, a deposit of metallic silver in the form of a mirror appears on the vessel walls:



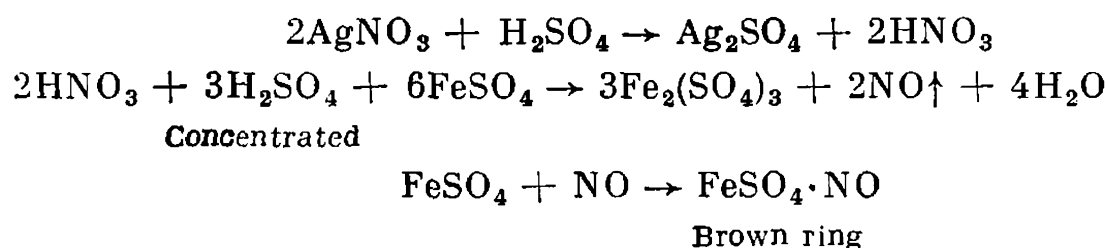
These two reactions are pharmacopoeial ones.

In addition to these reactions, the silver cation can be detected by a reaction with potassium chromate, which yields a reddish brown silver chromate precipitate:



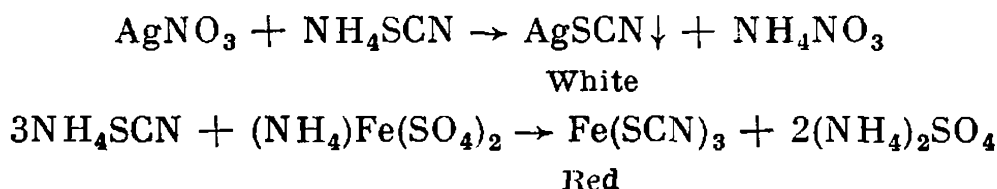
The precipitate is soluble in nitric acid and ammonium hydroxide, and is sparingly soluble in acetic acid.

The nitrate ion is determined with diphenylamine (a blue colour) and by the formation of a brown ring when silver nitrate is reacted with iron sulphate in concentrated sulphuric acid:



The good quality of the preparation is characterized by the tolerated acidity and the absence of salts of the heavy metals (lead, copper, bismuth).

The content of the preparation is determined by the Volhard method of precipitation:



The State Pharmacopoeia requires that the preparation contain at least 99.75% of pure silver nitrate.

Silver nitrate is used in medicine for the cauterization of wounds and ulcers in the form of rods (*Stilus Argenti nitrici*). Its cauterizing action is due to the ability of silver nitrate to coagulate proteins and transform them into insoluble compounds.

In small concentrations, silver nitrate has an astringent and anti-pyretic action.

It is administered externally in erosions, ulcers, in acute conjunctivitis, and trachoma in the form of 2-5-10% aqueous solutions, and also of ointments (1-2%). It is prescribed orally in the form of a 0.05-0.06% solution for gastric ulcers and chronic gastritis.

The highest single oral dose for adults is 0.03 g, the highest daily dose is 0.1 g.

All silver salts are poisonous and are listed in Group A. They must be stored locked up in well closed orange glass jars with ground glass stoppers in a place protected from light.

REVIEW QUESTIONS

1. What explains the high reactivity of Group I elements relative to electro-negative elements?
2. What properties of silver preparations are used in medicine?
3. Why must silver nitrate be stored in orange glass jars and in a place protected from light?

PRACTICAL LESSON

Analysis of a 2 % Silver Nitrate Solution

1. Write the prescription in Latin.
2. Perform an identification reaction:
 - (a) add a solution of diphenylamine in concentrated sulphuric acid to a part of the preparation solution in a porcelain bowl. A rapidly vanishing blue colour forms;
 - (b) add one or two drops of dilute hydrochloric acid to a part of the preparation solution. A white curdy precipitate forms that is insoluble in nitric acid and soluble in an ammonium hydroxide solution.
 Write the equations of the chemical reactions.
3. Carry out a quantitative determination (the thiocyanometric method—express analysis).

Transfer 1 ml of the solution into an Erlenmeyer flask for titration, add six drops of an ammonium iron alum indicator, and titrate with a 0.1 *N* solution of ammonium thiocyanide up to a pinkish-brown colour.

 Write the equations of the reactions.
4. Calculate the silver nitrate content in the solution in per cent by formula (1.1):

$$X = \frac{VKT}{a} \times 100 = \frac{VK \times 0.01699}{1.0} \times 100$$

where *V* is the volume of a 0.1 *N* ammonium thiocyanide solution, ml, *T* = 0.016 99 g/ml, and *a* is the volume of the preparation taken for titration, ml.

5. Compare the result obtained with the prescription and conclude whether the medicinal substance may be dispensed.

Chapter 9. Group VIII Elements

Group VIIIA consists of the noble (previously called inert) gases having a very low chemical activity. Group VIIIB includes elements of triads, and its belonging to Group VIII is conditional, or historically traditional.

The first triad includes iron, cobalt, and nickel, the second—ruthenium, rhodium, and palladium, and the third—osmium, iridium, and platinum. They are all metals, most of which have two electrons in the outermost electron layer of an atom. These elements are characterized by oxidation states of +2, +3, and +4.

9.1. IRON COMPOUNDS

The most important Group VIII element from the medical viewpoint is iron. It occurs in nature in the form of silicates, oxygen compounds such as magnetite Fe_3O_4 , red iron ore (hematite) Fe_2O_3 , brown iron ore (limonite) $2\text{Fe}_2\text{O}_3 \cdot 3\text{H}_2\text{O}$, and in the form of sulphur compounds such as iron pyrite FeS_2 .

Pure iron has a grayish-white colour. It melts at a temperature above 1500°C . Iron is quite stable in dry air, but in humid air it rusts. Iron has magnetic properties. Dilute acids rapidly dissolve iron with the evolution of hydrogen.

The chemical properties of iron are characterized by its varying oxidation state. It can be $+6$, $+2$, and $+3$.

The iron(VI) oxide (acidic) is not stable and is of no significance for medicine.

The iron(II) oxide FeO is basic, while the iron(III) oxide Fe_2O_3 is amphoteric. The latter two oxides yield a number of salts that are employed in medicine.

There exist iron(II) (ferrous) and iron(III) (ferric) salts. The former are generally white or of a greenish colour, while the iron(III) salts are yellow or red brown. The iron(II) salts are not stable, they are readily oxidized by the oxygen of the air and turn brown. Iron is contained in the human organism, primarily in the haemoglobin of the blood.

The use of iron preparations in medicine is based on their astringent and cauterizing action depending on their concentration. Iron(II) is physiologically more active than iron(III). Iron preparations are chiefly administered for anaemia and also as a haemostatic (styptic).

Reduced iron is a pharmacopoeial preparation.

Reduced Iron (*Ferrum reductum*)

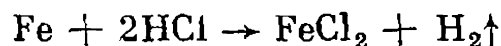
Fe

A.m. 55.85

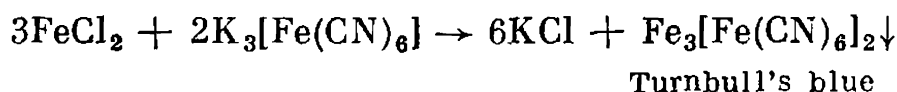
Reduced iron is produced at present by the electrochemical reduction of an aqueous solution of iron(II) sulphate in the presence of ammonium chloride at $20\text{--}40^\circ\text{C}$ at a voltage of $1.8\text{--}2.5\text{ V}$. Electrolysis of the solution is conducted at a strictly definite pH (3-4), which is monitored by adding sulphuric acid. The iron reduced at the cathode is removed, rinsed with water until the reaction for sulphates and chlorides is negative, and is dried at 50°C . Next it is triturated and screened. The resulting preparation contains 99% of iron.

Reduced iron is a fine, lustrous or dull powder of a gray or dark gray colour. It is attracted by a magnet. When heated, it glows and transforms into the black ferri-ferrous oxide Fe_3O_4 .

The preparation dissolves in acids with the formation of salts:



If potassium ferricyanide is added to the preparation dissolved in hydrochloric acid, a dark blue precipitate forms (Turnbull's blue). This is a reaction for iron in the oxidation state +2:



The iron used in medicine must be free of admixtures of copper sulphides, carbon, silicic acid, and arsenic. The State Pharmacopoeia tolerates impurities of heavy metals in the preparation not exceeding 0.01 %.

To determine the above impurities, the iron preparation is treated with hydrochloric acid. The iron dissolves completely in it, while the impurities remain undissolved. They are determined in the filtrate by the relevant analytical reactions.

The quantitative determination of the substance in the preparation is performed by permanganatometry, in which Fe^{2+} becomes oxidized to Fe^{3+} . A sample of reduced iron is dissolved in sulphuric acid with heating, and after cooling is titrated with a 0.1 *N* potassium permanganate solution until the pink colour stops vanishing:



The State Pharmacopoeia requires that the preparation contain at least 99% of pure iron.

The preparation is taken orally in acute anaemia as an agent acting on the haemopoietic organs and metabolism processes. It should be stored in well closed jars in a dry place.

REVIEW QUESTIONS

1. Which oxidation state is characteristic of iron?
2. Why must reduced iron be dissolved before conducting an identification reaction and quantitative analysis?
3. How can one explain why reduced iron is administered to treat anaemia?

III. Organic Drugs

Organic chemistry studies carbon compounds. Organic substances always contain carbon and hydrogen in their molecule. This is their main distinction from inorganic compounds.

Other elements such as oxygen, nitrogen, sulphur, phosphorus, halogens, and a number of separate groups may also be contained in molecules of organic compounds and form numerous derivatives of them.

Organic chemistry as a science took shape in the 19th century, but organic compounds were known to mankind back in ancient times. Thus, as long ago as in the 6th century, vinegar was produced from sour wine, alcoholic beverages—from saccharine substances, etheric substances and dyes—from plants, and so on.

The studying of organic compounds in their native form was begun by K. Scheele in the middle of the 18th century. He separated tartaric acid from grapes, citric acid from lemons, malic acid from apples, lactic acid from sour milk, oxalic acid from dock, and uric acid from the urine of animals. Many of the acids he separated and their salts are drugs that are still in use today. Later Scheele discovered glycerin—the basic component of all animal fats and vegetable oils.

Other chemists of that time separated urea from human urine, hippuric acid from horse urine, and cholesterol, which became a source for the preparation of valuable drugs, from animal tissues.

In 1824, the German chemist F. Wöhler synthesized oxalic acid, and in 1828 urea. In the following years more complicated organic substances were synthesized such as fats (the French chemist P. Berthelot) and saccharine substances (A. Butlerov).

A major role in the further development of organic chemistry was played by the theory of chemical structure worked out by the eminent Russian scientist Butlerov. The theory of chemical structure enabled chemists to cognize the internal structure of a molecule, understand the essence of chemical processes, and predict new ways of synthesizing organic substances.

Chapter 10. Sources and Analysis

10.1. SOURCES

Arboreal flora is a rich source of organic substances. The dry distillation of wood yields, among others, wood vinegar and wood tar. The latter, in turn, is a raw material for the preparation of many drugs, for example, the phenols and their derivatives. Coal, various kinds of petroleum, combustible shale, etc. are very rich natural sources for the production of many drugs.

Organic drugs are also produced from plants from which alkaloids, glycosides, and vitamins are separated. Phytoncides have been isolated from substances that plants produce during their growth.

Raw materials of an animal origin are employed for the production of many hormones, vitamins, and enzymes. Antibiotics are mainly products of the vital activities of microorganisms.

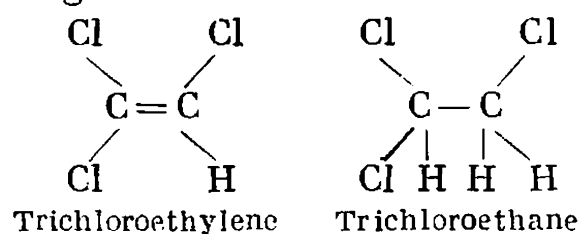
However, the natural sources contain biologically active substances (alkaloids, glycosides, hormones, vitamins, antibiotics, etc.) in very small amounts and therefore cannot completely cope with the requirements of practical medicine. In this connection, it became necessary to produce synthetic drugs whose action is similar to that of natural substances.

The multitude of drugs at the disposal of modern medicine was created and developed during a number of centuries. But the synthesis of medicinal agents developed the most during the last 40-50 years. At present, the search for new drugs is proceeding very intensively. Soviet scientists have achieved substantial success in the field of the synthesis of new drugs, chiefly chemotherapeutic ones. The medical industry of the USSR at present produces about 3000 various drugs.

The achievement in the synthesis of drugs is a result of the detailed study of the relation between the structure of a medicinal agent and its action on an organism. This problem, which is the cornerstone of the directed synthesis of drugs, came to the forefront over 100 years ago and is still being solved.

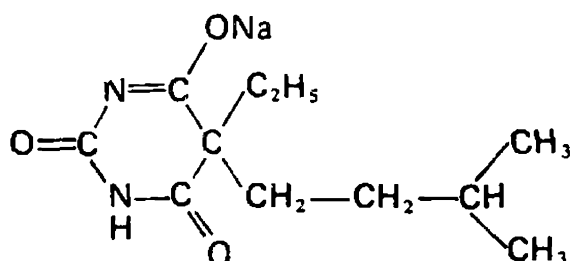
We shall give as examples only a few tenets on the relation between the chemical structure of organic substances and their pharmacological action.

Influence of unsaturated bonds. Unsaturated compounds are considerably more active than saturated ones. This relates both to aliphatic and aromatic compounds. For example, trichloroethylene is a stronger soporific agent than trichloroethane:

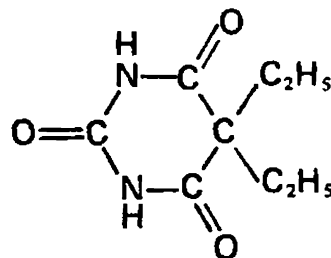


The introduction of an unsaturated bond into a molecule increases the narcotic effect. But this is attended by an increase in the toxicity of the substance.

Influence of a branched carbon chain. Branching of the carbon chain increases the physiological action of a preparation. For example, in the group of barbiturates (soporific agents), barbamy (amobarbital) is a more effective soporific than barbital:



Barbamy



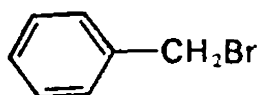
Barbital

Chain length. The physiological effect generally grows from C_1 to C_5 , then, beginning with six and more carbon atoms in a molecule, this effect decreases, and finally disappears. The explanation is that with an increase in the number of carbon atoms in a chain, the solubility of substances lowers. They do not get into the blood and fail to reach the corresponding centres, hence they do not cause the required effect.

Optical isomerism. It has been established that levorotatory isomers are often more active than dextrorotatory ones. It has also been established that isomers have a different effect on the taste endings (buds) and have a different action. For example, the dextro asparaginic and glutamic acids have a sweet taste, while their levorotatory isomers are tasteless.

Introduction of halogens. Halogen derivatives of both the aliphatic and aromatic series are more active than the parent hydrocarbons. For example, methane is not a narcotic, methyl chloride CH_3Cl has a slight narcotic effect, while ethyl chloride CH_3CH_2Cl and chloroform $CHCl_3$ have a more pronounced narcotic effect. It can also be seen that the number of halogen atoms introduced into a molecule matters. The same relates to compounds of the aromatic series.

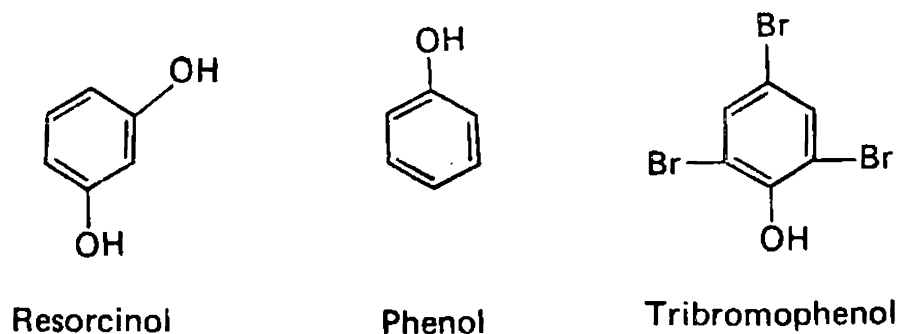
When the number of halogen atoms in a benzene molecule is increased, its toxicity lowers, but this is attended by a decrease in its physiological activity, which is probably due to diminishing of the solubility. For example, dichlorobenzene is more toxic than trichlorobenzene. The introduction of chlorine or bromine into a side chain results in the formation of lacrimators, for example, benzyl bromide:



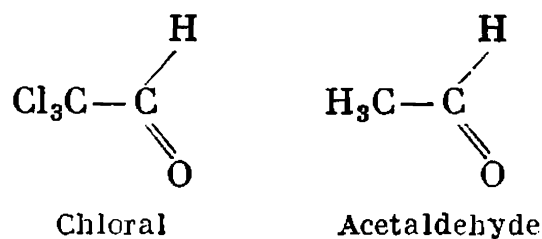
Introduction of hydroxyl groups. The substitution of hydroxyl for hydrogen in a molecule of a substance increases the physiological effect of the preparation. Thus, the narcotic effect of alcohols is stronger than that of the corresponding hydrocarbons. Secondary alcohols act more strongly than primary ones, and tertiary alcohols, more strongly than secondary ones.

The introduction of hydroxyl into benzene gradually reduces its antipyretic action; phenol still has a weak antipyretic effect, but it also exhibits a new property—antiseptic, and in diatomic phenols this property increases to a still greater extent. For example, resorcinol is a stronger antiseptic than phenol.

Tribromophenol is a still better antiseptic than the preceding two compounds, i.e. the antiseptic action is boosted by introducing bromine into the nucleus:



Introduction of a carbonyl group ($>\text{C}=\text{O}$). This increases the physiological effect of a compound. Numerous examples reveal that aldehydes and ketones are more active physiologically than the relevant hydrocarbons. The activity grows still more if a halogen atom is introduced into a molecule. For example, chloral has a stronger hypnotic effect than acetaldehyde:



Introduction of a carboxyl group ($-\text{COOH}$). This substantially lowers the poisonous properties of a substance. Organic acids of both the aliphatic and aromatic series have a low toxicity. This is witnessed by their widespread occurrence in nature and the inclusion of many of them in food products.

The hydrogen of the carboxyl group can become detached owing to dissociation of the molecule and is responsible for the cauterizing and to a certain extent irritating effect of the acids. This property is absent in their salts, where the carboxyl hydrogen is replaced with a metal cation.

The introduction of a carboxyl group into a molecule also changes certain physical properties of the relevant substance. For instance, benzene is absolutely insoluble in water, while benzoic acid has a slight solubility. The latter grows still more when the free acid is transformed into a salt, especially of an alkali metal or an organic base.

Introduction of an amino group. The introduction of this group results in an increase in the antipyretic properties, for example, aniline has a clearly expressed antipyretic effect. At the same time, the amino group imparts toxicity to a compound. This is why aniline, as is well known, is not a medicinal preparation.

The simultaneous presence in an aromatic ring of an amino group and hydroxyl imparts anaesthetizing properties to a molecule. These properties are amplified still more by etherification of the hydroxyl:



The introduction of a nitro group ($-\text{NO}_2$) into an aromatic ring affects the breathing centre.

The introduction of a nitroso group ($-\text{N}=\text{O}$) facilitates the substance reaching a nerve centre responsible for blood vessel dilatation (amyl nitrite, sodium nitrite).

The above examples of how the chemical structure of a molecule affects its pharmacological action reflect only the fundamental classical laws of this relation, which are still being used by chemists. And every time when new compounds are obtained, new and new relations between the chemical structure and the pharmacological action are discovered. These relations open new roads to the purposeful synthesis of drugs.

Initially, the main attention was devoted to the chemical structure of a substance, but later it became evident that any change in the structure of a molecule is attended by a change in the physicochemical properties of the relevant substance, and consequently in its action on the organism. It was established, for example, that the physicochemical properties of a substance affect its absorbability (passage through membranes) and its distribution in tissues, and this, in turn, influences its action on an organism.

This is why at present when creating new drugs and modifying existing ones, account is taken not only of the structural elements of a compound, but also of their influence on the physicochemical properties of the molecules (basicity, hydrophilic properties, degree of ionization, polarity, etc.).

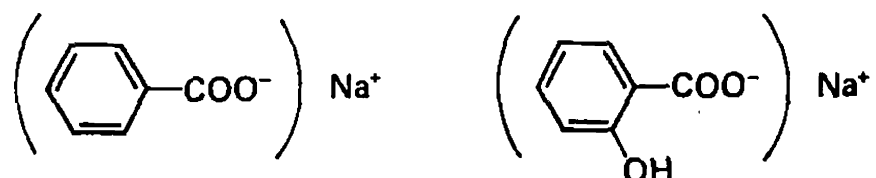
However, the above laws governing the influence of the chemical structure of a substance and its physicochemical properties on its physiological activity at present can no longer be the only basis for the purposeful synthesis of drugs.

The development of modern biochemistry and especially of patho-biochemistry enables one to establish the biochemical basis of a disease and reveal the mechanism of the biological activity of drugs, i.e. determine the biosubstrates in an organism with which a drug interacts and thus renders a healing effect.

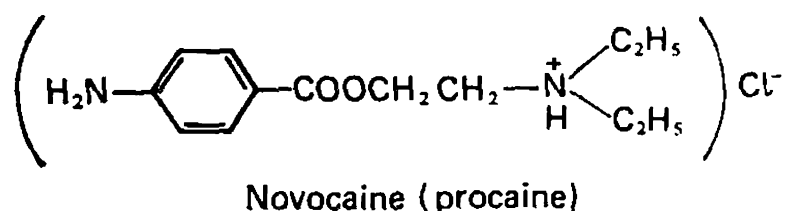
10.2. FEATURES OF ANALYSIS

The methods used for analysing organic drugs differ from those for inorganic ones and have special features.

Unlike inorganic compounds, most organic ones are not electrolytes, therefore reactions of the ionic type cannot be used for them. Exceptions are (a) salts of organic acids:



and (b) salts formed by organic bases and mineral acids, which dissociate into ions:

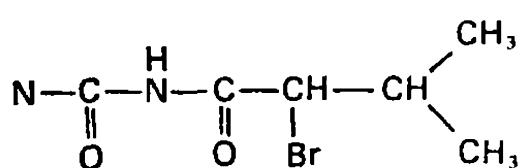


Whereas reactions between inorganic compounds generally proceed instantaneously because of exchange between the ions, reactions between organic substances generally proceed slowly, and they can often be stopped at the stage of formation of intermediates, i.e. a series of transformations between the initial and final results can be observed. At the same time, all organic compounds are to a certain extent unstable at high temperatures, and with strong heating they burn completely.

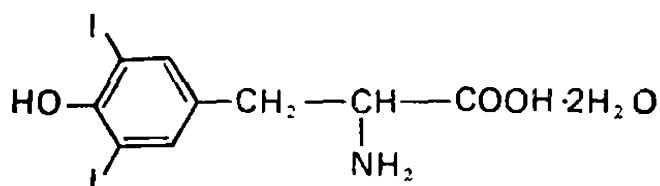
To determine whether a given substance belongs to organic compounds, it is essential first of all to see whether carbon is present in it. This is sometimes quite simple, because many organic substances when roasted become carbonized, i.e. transform into a coal, and this confirms the presence of carbon. But in many cases organic substances do not become carbonized when roasted. For example, if alcohol is heated, it can evaporate, while if it ignites, it burns without any residue.

Therefore, the most reliable way of detecting carbon in an organic compound is the burning of this compound with an oxidizing agent.

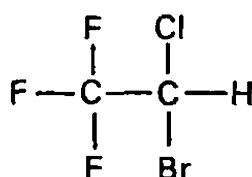
In addition to carbon and hydrogen, an organic molecule can contain other elements such as the halogens Cl, Br, F, and I:



Bromisoval



Diiodotyrosine



Ftorotan

A glance at the above formulas reveals that the halogen in the molecules of bromisoval, diiodotyrosine, and ftorotan (halothane) is bound directly to the carbon (a covalent bond). Such compounds do not dissociate into ions, and therefore the halogen in a molecule cannot be directly determined by the usual analytical reactions (for example, with a silver nitrate solution).

In this case to detect the halogen in a molecule, it has to be transferred into an ionogenic state. For this purpose, the organic substance must first be destroyed. This process is called **mineralization**, and it is conducted in various ways such as combustion, oxidation, heating with alkalis, and fusion with alkali metals. Mineralization yields simple inorganic substances in the form of hydrohalic acids or salts (halides) that dissociate and can be detected by the conventional ionic analytical reactions.

The products of mineralization of an organic substance must include CO_2 and H_2O , which point to the organic nature of the substance.

Of major significance in the analysis of organic drugs is the determination of the relevant physical and chemical indices. They are needed not only for identification, but also as a criterion of the purity of the drugs. For example, one of these indices for solids is their melting point. Liquids are characterized by their boiling point, specific gravity or density, and refractive index.

These indices are definite only for pure substances. When a solid drug contains an impurity, its melting point lowers, while in a liquid drug the boiling point in the course of distillation continuously grows.

The refractive index, which is constant for a pure substance, can deviate very greatly in the presence of impurities. But it is not sufficient to determine these indices for organic drugs. They give only an approximate preliminary notion of the nature of a drug. For the reliability of analysis, it is necessary to perform a chemical analysis in addition to the determination of the physicochemical indices.

A feature of organic drugs is the presence in their molecules of **functional groups**, i.e. reactive atoms or groups of atoms determined by chemical reactions. Functional groups determine the way of analysing organic drugs because they are responsible for the properties of substances and determine the identification reactions and the methods of quantitative determination of a drug.

Knowing the reactions for detecting functional groups, one can easily and conscientiously analyse any organic drug with a complicated structure. There are very many functional groups (about 100), and the molecules of most drugs have a polyfunctional nature, i.e. simultaneously contain several functional groups.

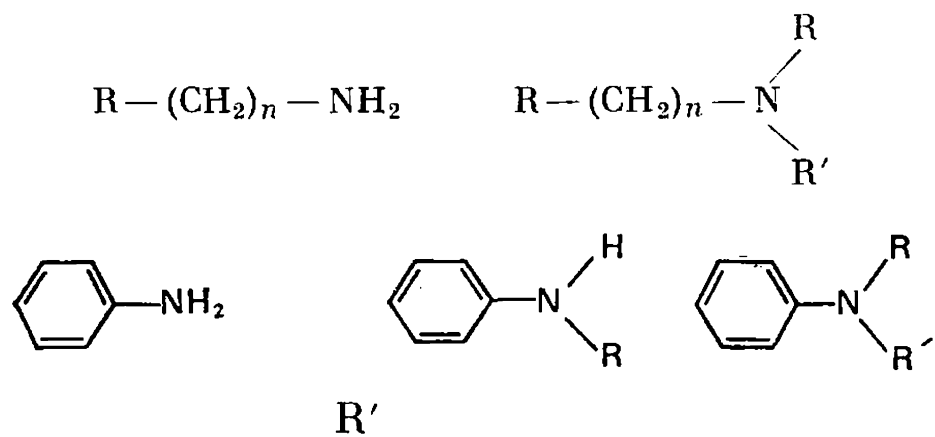
Functional groups can be combined according to their common properties and be classified with a view to three main properties:

(1) functional groups imparting an acidic nature to a substance, namely, the carboxyl ($-\text{COOH}$), imide (>NH), sulphhydryl or thiol ($-\text{SH}$), enol [$\text{>C}=\text{C}(\text{OH})$], enediol ($-\text{C}=\text{C}-$), and phenol

$$\begin{array}{c} \text{OH} \quad \text{OH} \\ | \quad | \\ -\text{C}=\text{C}- \end{array}$$

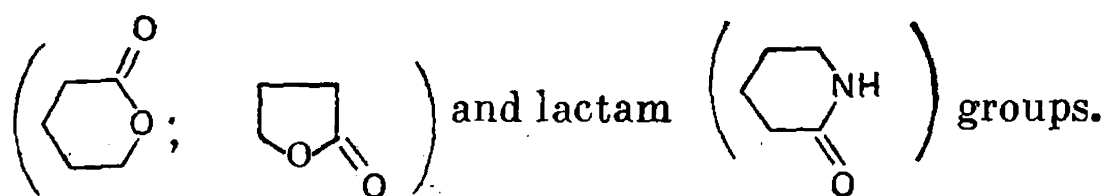
hydroxyl ($\text{>C}=\text{C}-\text{OH}$) groups;

(2) functional groups imparting basic properties to a substance, namely, a primary amino group (in aliphatic and aromatic compounds), free and substituted:



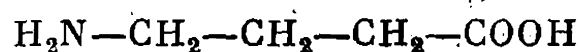
a tertiary amino group ($\text{R}-\text{N}-\text{R}''$) (the tertiary nitrogen is a necessary element in molecules of alkaloids and heterocyclic compounds), and a hydrazine group ($\text{H}_2\text{N}-\text{NH}_2$);

(3) functional groups exhibiting neither acidic nor basic properties, namely, an aldehyde ($\text{—}\overset{\text{O}}{\underset{\text{||}}{\text{C}}}\text{—H}$), keto ($\text{S—}\overset{\text{O}}{\underset{\text{||}}{\text{C}}}\text{—R'}$), methoxy (OCH_3), hydroxymethyl or primary alcohol (RCH_2OH), nitroso (—N=O), ether (R—O—R'), and ester ($\text{—}\overset{\text{O}}{\underset{\text{||}}{\text{C}}}\text{—O—}$) groups, an unsaturated carbon bond (>C=C< ; $\text{—C}\equiv\text{C—}$), a lactone

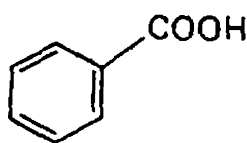


Let us consider as examples the reactions for some functional groups.

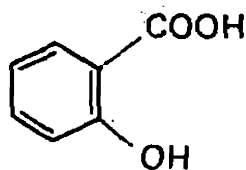
Carboxyl group (—COOH). Drugs belonging to the group of carboxylic acids can be of the aliphatic, aromatic, and heterocyclic series:



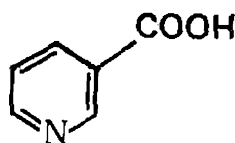
Aminalox (GABA)



Benzoic acid



Salicylic acid



Nicotinic acid

The carboxylic group in the molecules of the above carboxylic acids can be detected by the following reactions:

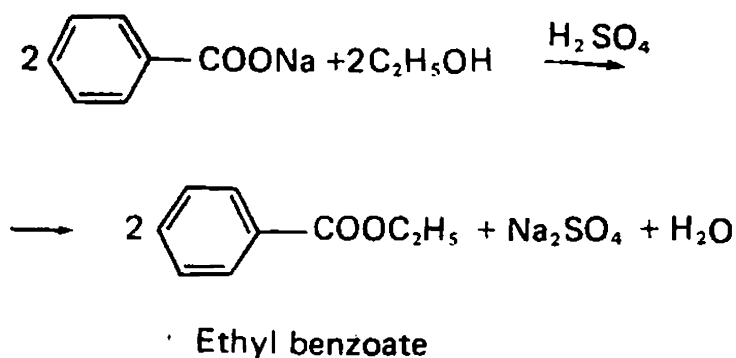
(1) a reaction of the medium (to litmus or some other indicator); aqueous or aqueous-alcohol solutions of carboxylic acids exhibit an acidic reaction to litmus or another corresponding indicator;

(2) a reaction with potassium iodate and iodide solutions; when a carboxylic acid is reacted with a mixture of potassium iodate and iodide solutions, iodine is evolved that colours the solution yellow, and when starch is added, blue:

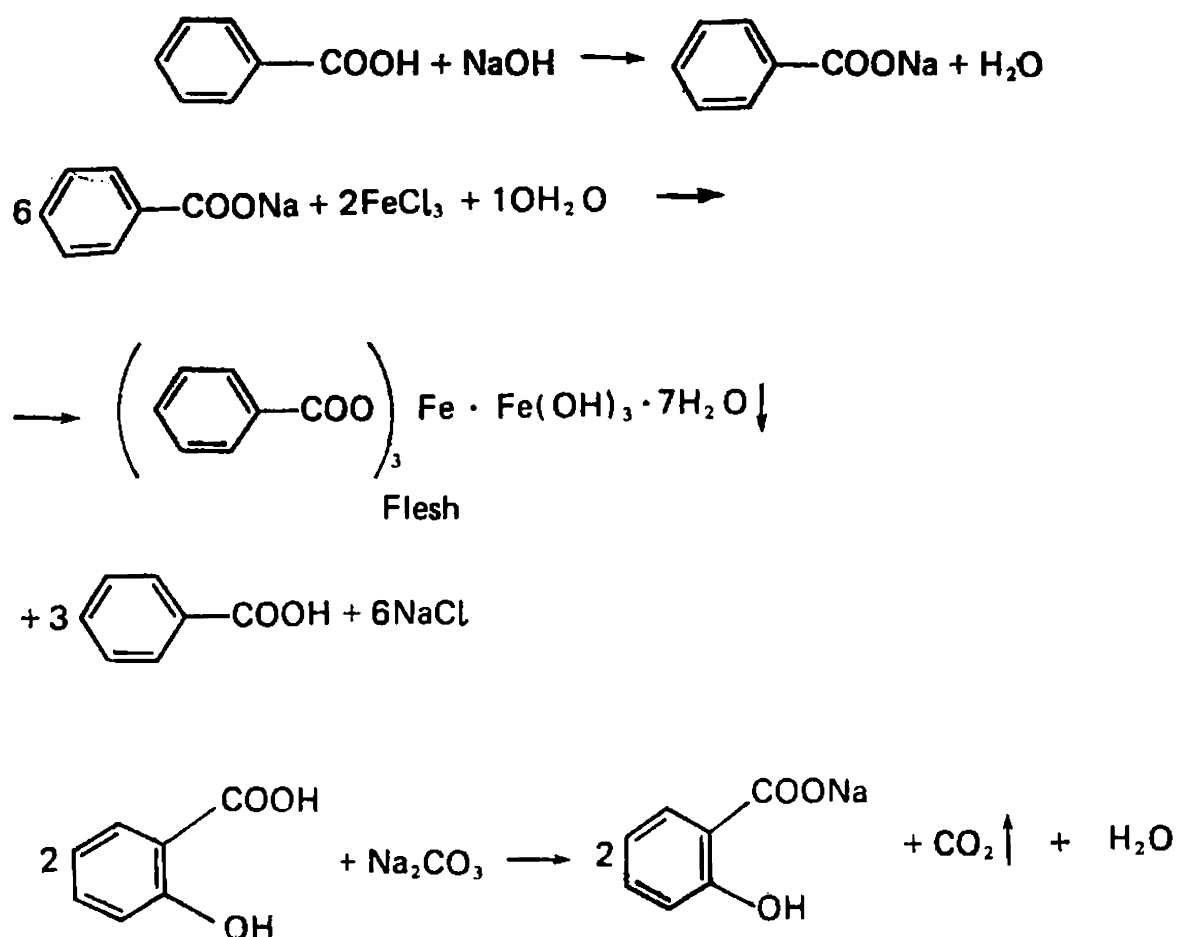


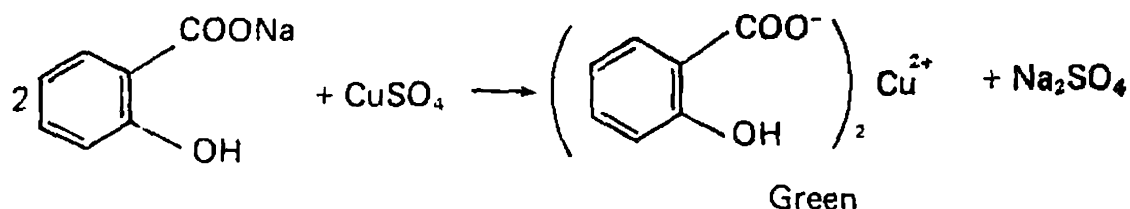
(3) the formation of esters; a small amount of the acid or its salt is dissolved in water, an equal volume of concentrated sulphuric acid (a dehydrating agent) and a few drops of ethyl alcohol are added.

Heating of the mixture produces a fruit odour of the formed ester (ethyl benzoate):



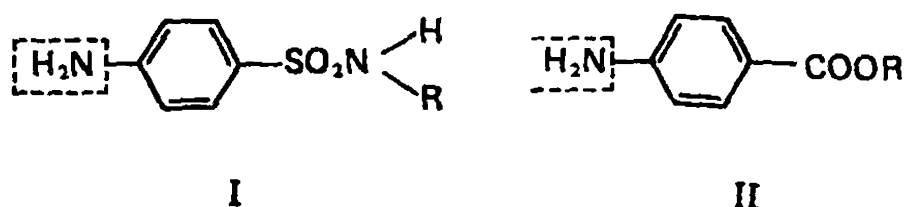
(4) reactions with salts of the heavy metals (CuSO_4 , CoCl_2 , FeCl_3 , etc.); carboxylic acids and their salts form coloured solutions or precipitates with solutions of heavy metal salts, and this is used for identification. When dealing with a free carboxylic acid (for example, benzoic), it has to be first neutralized with a 0.1 *N* solution of sodium hydroxide (using phenolphthalein) up to a faint pink colour, after which the heavy metal salt solution is added. If a salt of a carboxylic acid is being identified, for example, sodium benzoate, the heavy metal salt solution should be added to its solution directly. In both cases, either a coloured precipitate or a coloured solution forms whose colour depends on the nature of the acid and the reagent:





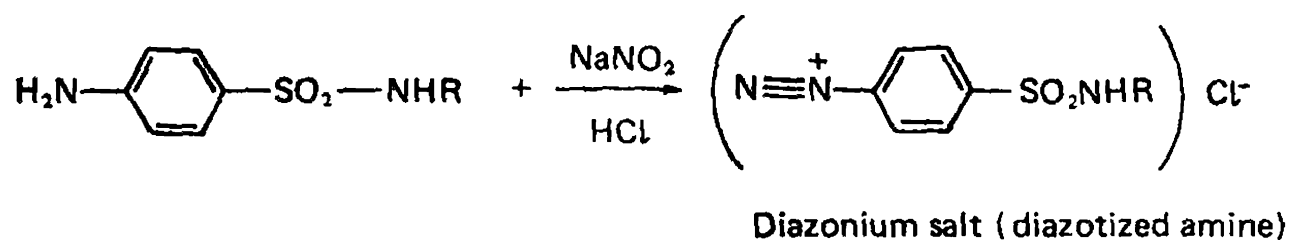
Amino group in an aromatic ring $\left(\text{C}_6\text{H}_5\text{NH}_2 \right)$. An aromatic ami-

no group is encountered quite frequently in molecules of drugs. For example, it is contained in molecules of sulphanilamide preparations (I), and in esters of *para*-aminobenzoic acid, in the group of local anaesthetics (II):

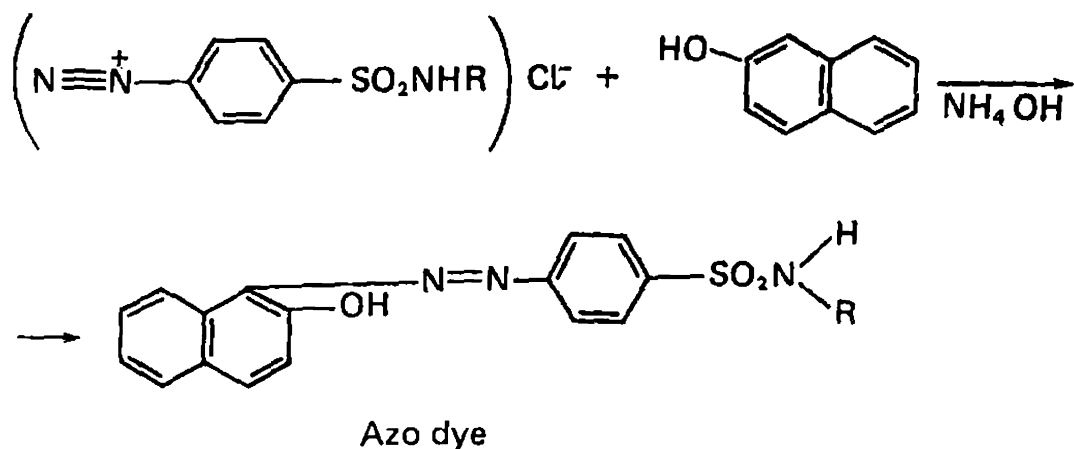


An amino group in aromatic compounds is determined by the following reactions:

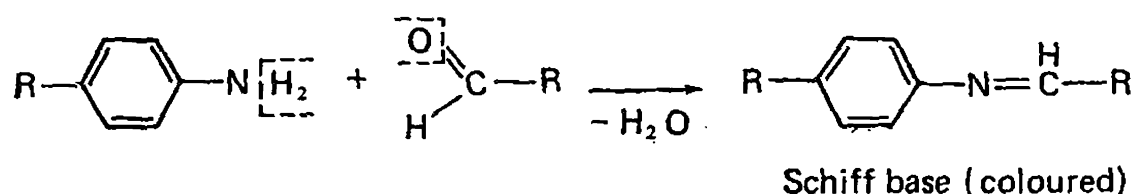
(1) a reaction of azo dye formation; aromatic amines in an acidic medium when reacted with sodium nitrite readily form colourless or pale yellow salts of diazonium, which when reacted with phenols in an alkaline medium form azo dyes. Since the latter are close in colour regardless of the nature of the aromatic amine, this reaction is a group one for all primary aromatic amines:



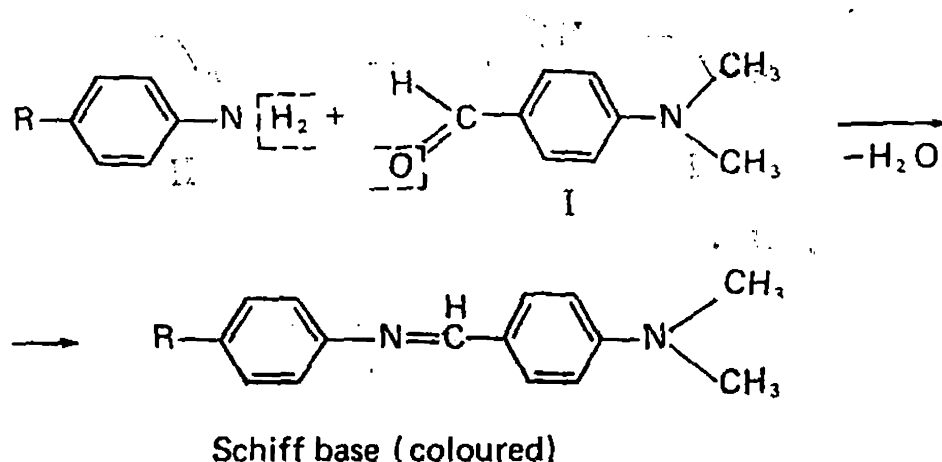
Next the diazonium salt is combined with 2-naphthol or another phenol. A diazonium salt combines with a phenol first of all in the *para*-position relative to the phenol hydroxyl, and if it is occupied, in the *ortho*-position:



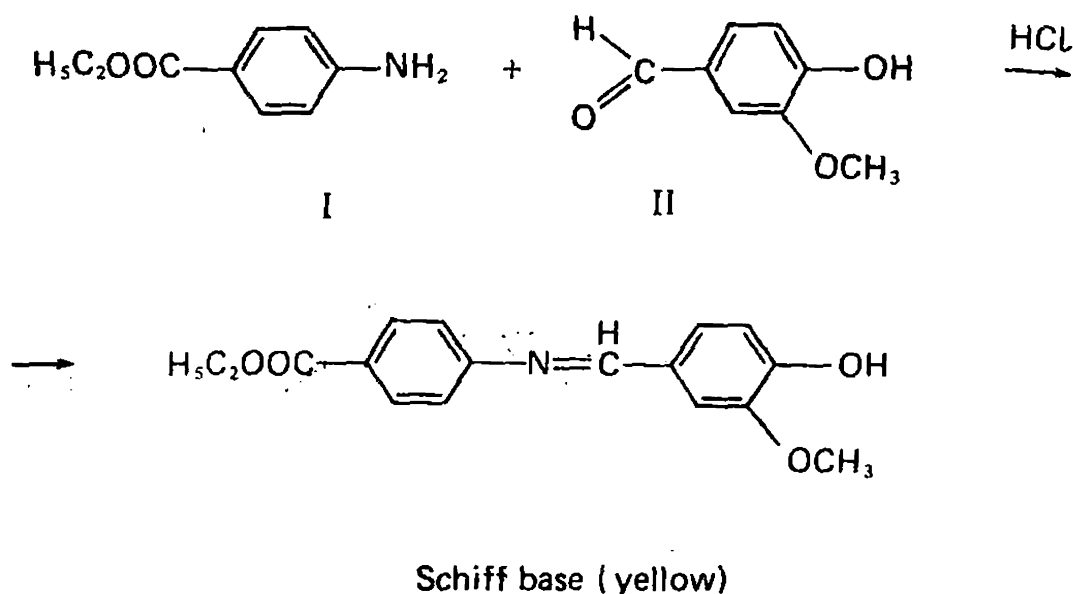
(2) a condensation reaction with aldehydes; drugs containing a primary amino group in their molecule react with aldehydes in an acidic medium with the formation of coloured condensation products:



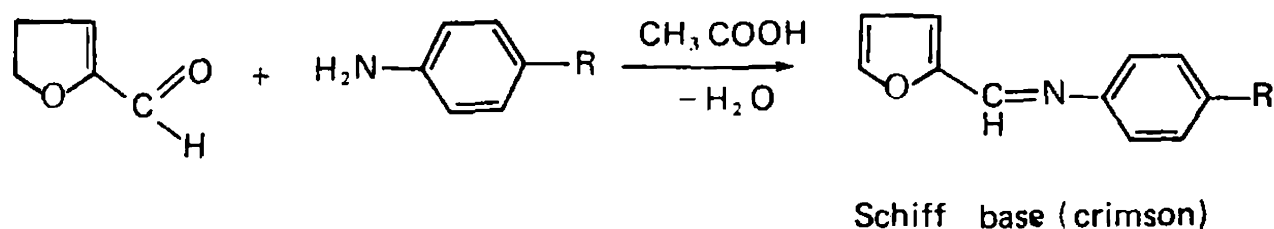
The State Pharmacopoeia often recommends *para*-dimethylaminobenzaldehyde (I) as the aldehyde; it yields coloured products when reacted with aromatic amines in the presence of hydrochloric acid:



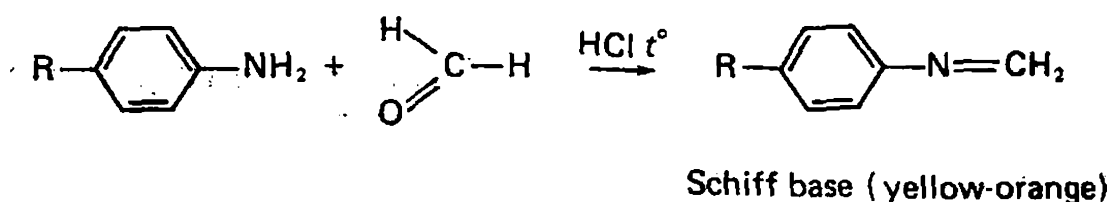
Other aldehydes can also be used for the identification of primary amines. Depending on the nature of the aldehydes, the formed condensation products (Schiff bases) have various colours. For example, to identify anesthesin (benzocaine) (I), vanillin (II) is often used:



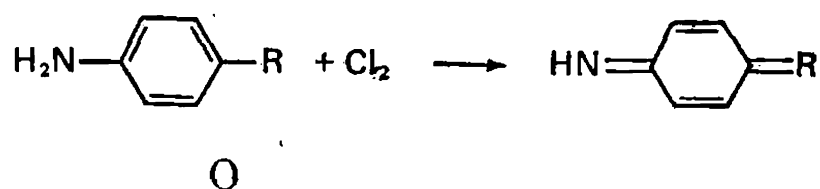
Other aldehydes when condensed with aromatic amines yield condensation products having other colours:



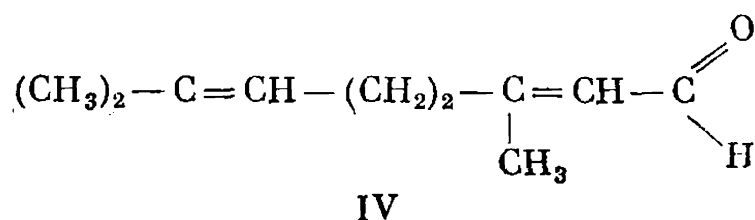
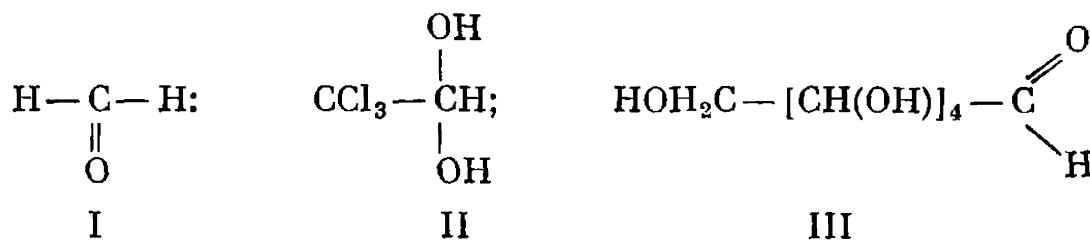
Condensation products in the form of yellow-orange or pink precipitates form when formalin is added in the presence of hydrochloric acid and the mixture is heated on a boiling water bath:



(3) an oxidation reaction; several primary amines of the aromatic series are readily oxidized with the formation of coloured oxidation products. Chloroamine or chlorinated lime is used as the oxidizing agent; the oxidizing effect is produced by the active chlorine which they evolve in an acidic medium. Potassium dichromate $\text{K}_2\text{Cr}_2\text{O}_7$ is also employed as an oxidizing agent in an acidic medium:

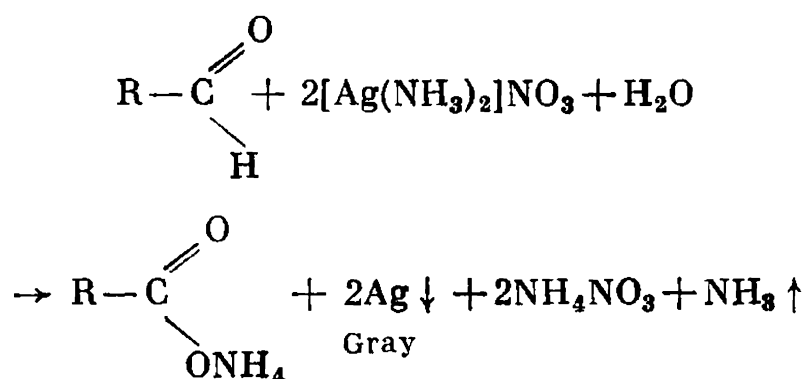


Aldehyde group ($-\overset{\text{O}}{\underset{\text{H}}{\text{C}}}-$). The drugs containing an aldehyde group in their molecule include formalin (a solution of formaldehyde in water) (I), chloral hydrate (a hydrate form of trichlorethylidene glycol) (II), glucose (III), and citral (IV):



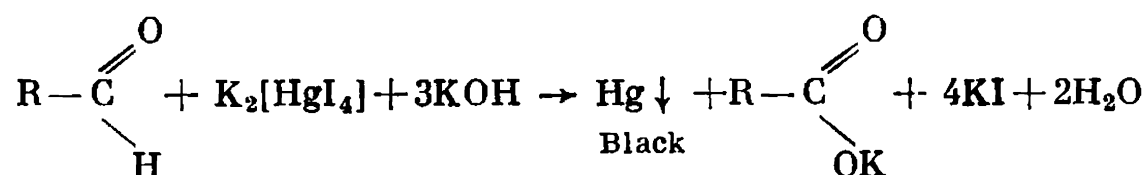
To identify the aldehyde group in these compounds, advantage is taken of its ability to be readily oxidized and exhibit reducing properties. Characteristic reactions of this type are:

(1) the reduction of silver from an ammonia solution of silver nitrate (the formation of a silver mirror):

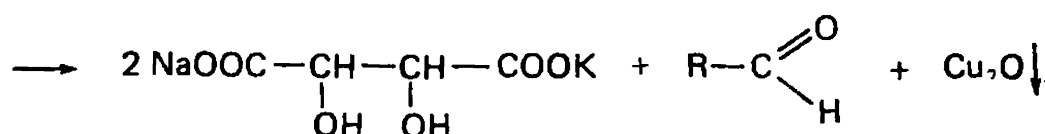
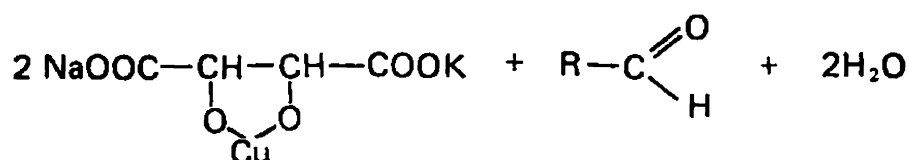
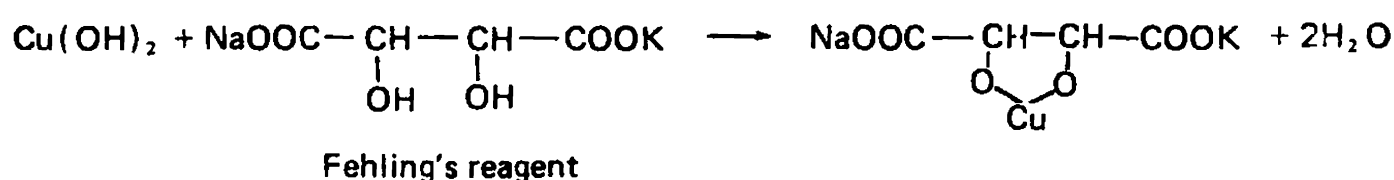
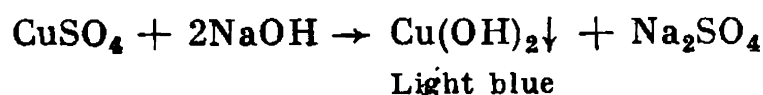


The metallic silver separates in the form of a gray precipitate or a silver deposit on the test tube (a silver mirror);

(2) a reaction with Nessler's reagent:



(3) a reaction with Fehling's reagent; Fehling's solution is added to a solution of the analyte preparation and the mixture is heated; a brick red copper(I) oxide precipitate gradually forms:



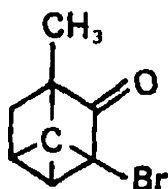
To identify an aldehyde group in a molecule, one can also use a condensation reaction with aromatic amines, as a result of which a coloured Schiff base forms.

When a molecule of a drug simultaneously contains other functional groups in addition to those indicated above, they must also be detected by the relevant reactions.

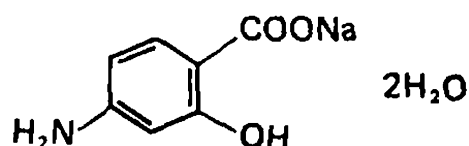
We shall consider reactions for other functional groups on following pages when treating individual groups of drugs.

REVIEW QUESTIONS

1. What is the main distinction of organic drugs from inorganic ones? What is the main feature of this distinction?
2. What is the main difference between analysing organic drugs and inorganic ones?
3. What physicochemical indices are characteristic for identifying organic drugs?
4. How can bromine be detected in a camphor molecule:

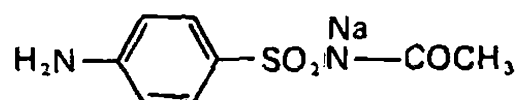


- Can it be detected by the direct action of a silver nitrate solution?
5. Name the functional groups responsible for an acid nature of a substance.
 6. Single out the functional groups in a molecule of the drug PAS-Na (sodium aminosalicylate) and name them:

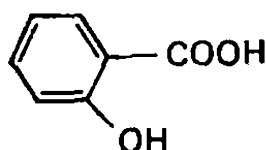


Which of them determine the basic nature of the drug and which, the acidic nature?

7. Using the drug sulphacyl-sodium (sulphacetamide sodium) as an example, indicate the possible identification reactions for the aromatic amino group:



8. Name the functional groups in a molecule of salicylic acid and indicate the reactions that can be used to confirm the presence of the carboxyl group:



9. Name drugs containing an aldehyde group in their molecule. What property of aldehydes are used in the reactions of their identification? Write them.

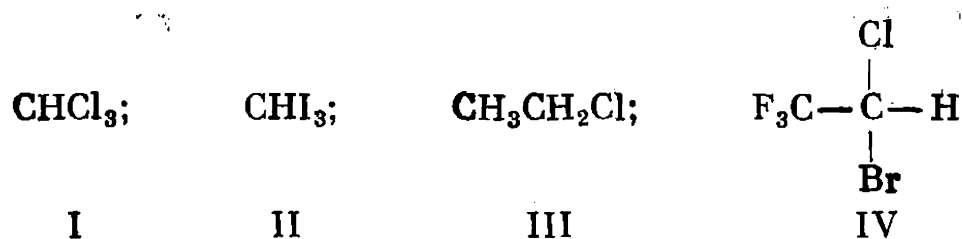
Chapter II. Halogen Derivatives of Aliphatic Hydrocarbons

Hydrocarbons in whose molecules one or more hydrogen atoms are replaced by a halogen have found application in medicine. Any of the four halogens (fluorine, chlorine, bromine, and iodine) can be present in a molecule of such compounds. They are sometimes present simultaneously, but each of them has its special effect on the chemical, physical, and pharmacological properties of the relevant compound.

The physiological action of halogen derivatives of hydrocarbons is due to the fact that they can dissolve in fats and cause physical and colloidal changes in the lipoids of the nerve tissues and thus produce an anaesthetic effect.

The intensity of the narcotic action of hydrocarbon halogen derivatives and their toxicity depend on the degree of halogenation of a hydrocarbon.

The following preparations from this group of compounds are used in medicine: chloroform (I), iodoform (II), ethyl chloride (chloroethane) (III), and ftorotan (halothane) (IV):



These formulas show that the first two preparations—chloroform and iodoform—are methane derivatives, while the other two—ethyl chloride and ftorotan—are ethane derivatives. All these preparations are pharmacopoeial.

They are all reactive chemically. The halogens in their molecule can be substituted by various radicals. However, the halogen is firmly bound to the carbon atom (except for iodoform) and is not ionogenic. To detect a halogen, first mineralization must be used, and only after this can the halogen ion be determined by conventional analytical reactions.

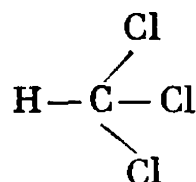
Ethyl chloride, chloroform, and ftorotan are volatile substances. They are administered for inhalation narcosis.

Ethyl chloride is also featured by its very low boiling point, from 12 to 13 °C, as a result of which it rapidly evaporates and causes strong cooling of the surface of a tissue. This makes it possible to use it for local anaesthesia in simple and brief operations (panaritium, etc.).

Iodoform is employed externally as an antiseptic. This property is due to the fact that the iodine in the molecule is not bound firmly to the carbon, is readily detached, and produces an antiseptic effect.

Chloroform (*Chloroformium*)

Trichloromethane



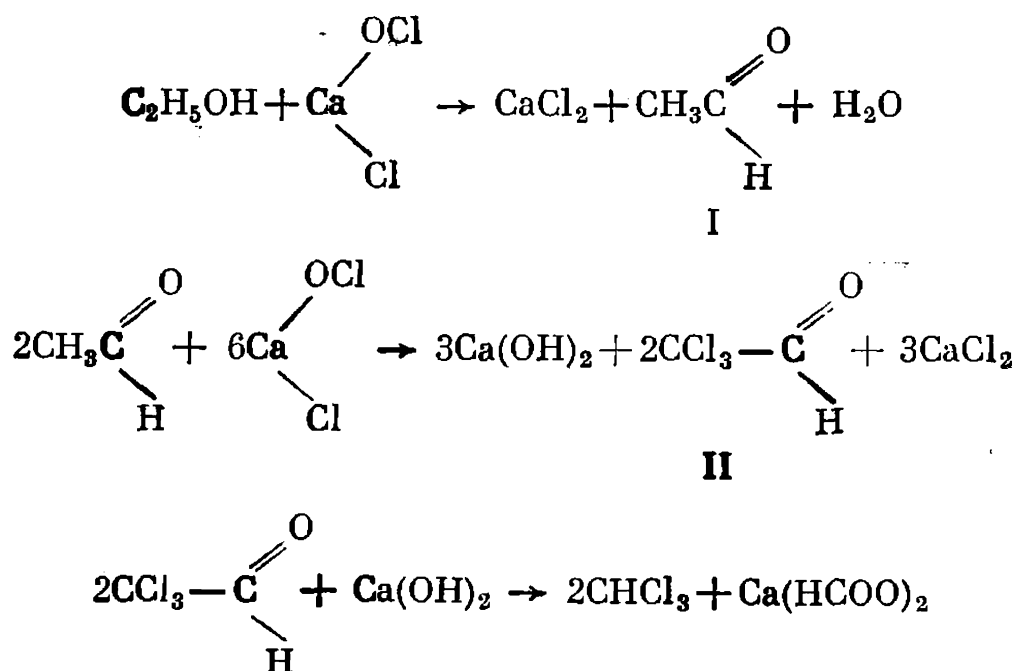
CHCl_3

M.m. 119.38

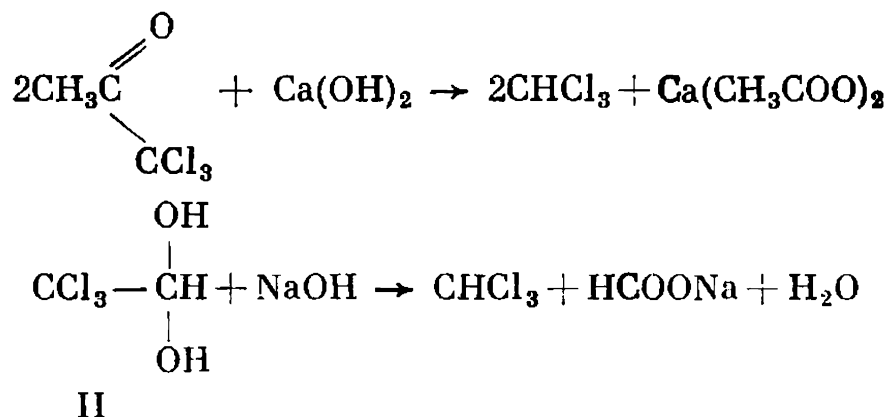
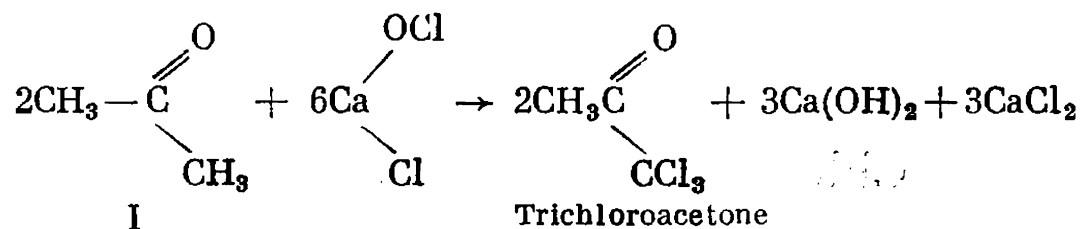
Chloroform was first used for narcosis in surgical operations by the Scottish obstetrician J. Simpson (1848). In Russia, chloroform as an agent for general narcosis was first used by N. Pirogov.

The State Pharmacopoeia lists two chloroform drugs, namely, chloroform, and chloroform for narcosis (*Chloroformium pro narcosi*), which is specially purified and is intended for inhalation narcosis. Their main difference is in the degree of purity. The methods of preparation, chemical properties, and identification reactions are the same for both drugs.

Preparation. For a long time, the most widespread industrial method of producing chloroform was the oxidation of alcohol by chlorinated lime to acetaldehyde (I), which was further oxidized by the chlorinated lime to trichloroacetaldehyde, or chloral (II). The latter when reacted with an alkali evolves chloroform:

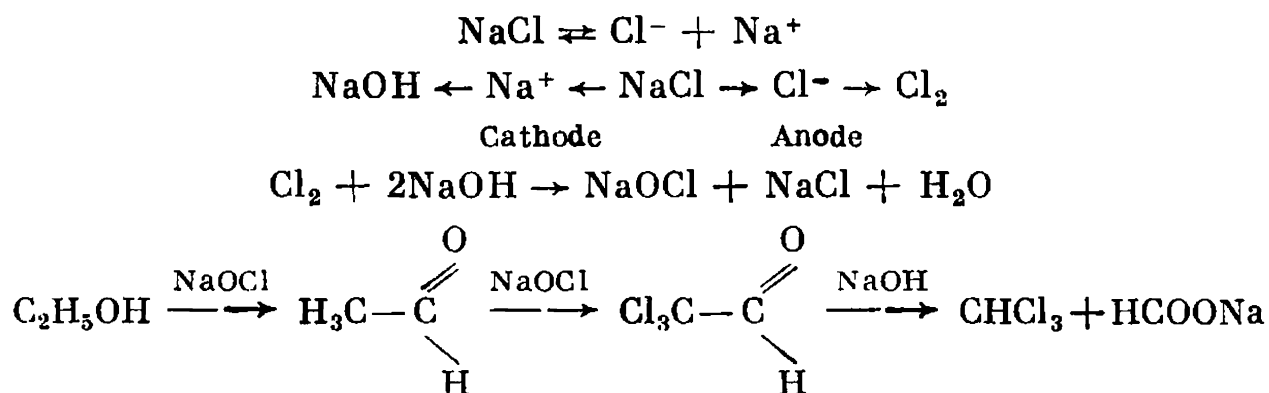


To produce chloroform with a higher purity, acetone (I) or chloral hydrate (II) is used instead of alcohol:



In both cases, the evolved chloroform is separated, washed with sulphuric acid, dried with calcium chloride, and distilled.

The modern way of producing chloroform is the electrolytic one, based on the same principle as the preceding methods. The initial substance is also alcohol or acetone. The alcohol or acetone is mixed with a solution of potassium or sodium chloride, the mixture is placed in the apparatus, heated to 60 °C, and subjected to electrolysis (using a current of three or four amperes). Electrolysis causes the sodium chloride to transform into sodium hypochlorite and hydroxide NaOCl and NaOH, which react with the alcohol (or acetone). The electrolysis process can be depicted schematically as follows:



The chloroform produced by any method is technical, which is not suitable for medicinal purposes and must be purified.

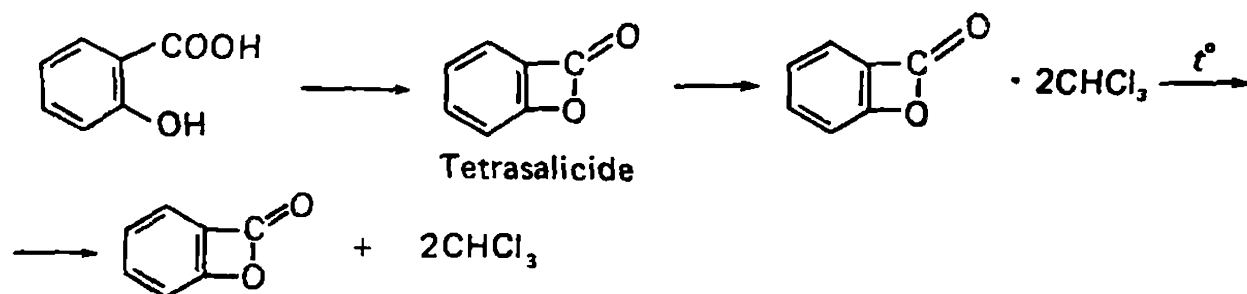
Purification. The first step in the purification of chloroform is to wash it with water by agitating it for one-and-a-half hours. After letting the impurities settle, the chloroform is decanted, and a small amount of 40% formalin and concentrated sulphuric acid is added to it. After stirring, the mixture is allowed to stand for a while. Next

the upper chloroform layer is separated from the lower one (organic impurities extracted by the sulphuric acid), washed with water, the residual sulphuric acid is neutralized with an alkali, and then the chloroform is distilled.

The distilled chloroform is passed through a filter with roasted potash, and the pure chloroform is collected in carboys into which alcohol is first poured in an amount of 1% of the mass of the chloroform.

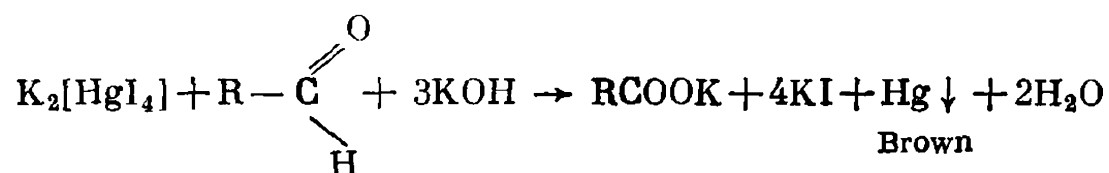
The carboys (usually with a capacity of 15 kg) are filled up to their top. A sample is taken from each carboy for analysing the chloroform and establishing its grade. The chloroform purified in this way is sufficiently pure, but is not yet suitable for narcosis.

The chloroform intended for narcosis must be additionally purified. For this purpose, a complex compound of chloroform in the crystallized form is obtained, which when heated on a water bath evolves chloroform, but with a higher purity. Generally tetrasalicide, i.e. salicylic acid anhydride, is used for this purpose. It crystallizes with two chloroform molecules in the form of a double salt. The tetrasalicide evolved in heating can be recycled into the production process. The obtained chloroform must meet all the requirements of the State Pharmacopoeia for narcotic ether:



Detection of impurities. But no matter how well chloroform has been purified, it can contain various admixtures such as aldehydes, organic impurities, chlorides, free chlorine, hydrochloric acid, alcohol, and water. The most dangerous admixture, especially in chloroform for narcosis, is phosgene. The origin of these admixtures is not accidental.

An admixture of aldehydes may be present in chloroform as a residual product in the process of its manufacture. An aldehyde is detected by using Nessler's reagent (a brown colour owing to the separation of free mercury):



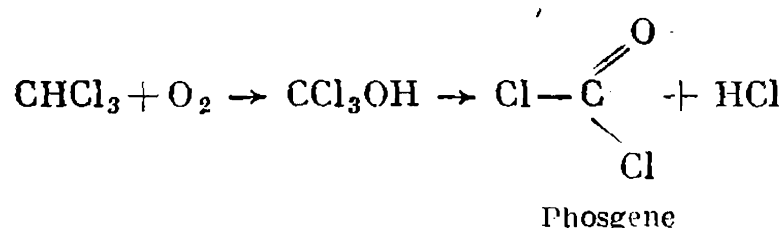
In the process of chloroform preparation, products of incomplete chlorination of the acetaldehyde or acetone may form, i.e.

$\text{CH}_2\text{Cl}-\overset{\text{O}}{\parallel}\text{C}-\text{H}$ and $\text{CHCl}_2-\overset{\text{O}}{\parallel}\text{C}-\text{H}$. These products in an alkaline medium can form various unsaturated compounds that increase the toxicity of the chloroform.

This is why the State Pharmacopoeia requires a test for organic impurities to be performed by adding concentrated sulphuric acid to the chloroform solution. The acid transforms any organic impurities present into tar, and the solution turns yellow.

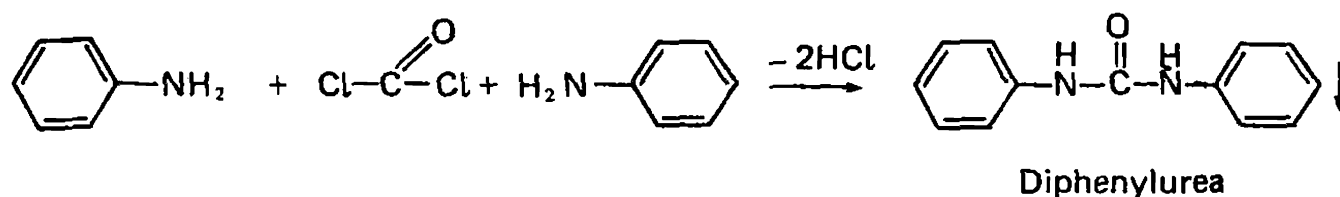
Chlorides (CaCl_2 , NaCl) that may form in the production of chloroform are detected by reacting the preparation with a silver nitrate solution.

The most dangerous impurity in chloroform, especially in that intended for narcosis, is phosgene. It can form in the preparation as a result of its oxidation by the oxygen of the air if proper storage conditions are not observed:



This process is intensified in the light and in the presence of moisture.

When chloroform contains an admixture of phosgene, the medium is acidic owing to the hydrochloric acid formed together with the phosgene. The acid is detected by the relevant indicator, for example, bromophenol blue. An admixture of phosgene in chloroform can be detected (a) by a reaction with aniline (the insoluble compound diphenylurea forms):



(b) by a reaction with benzidine $\left(\text{H}_2\text{N}-\text{C}_6\text{H}_4-\text{C}_6\text{H}_4-\text{NH}_2 \right)$ which

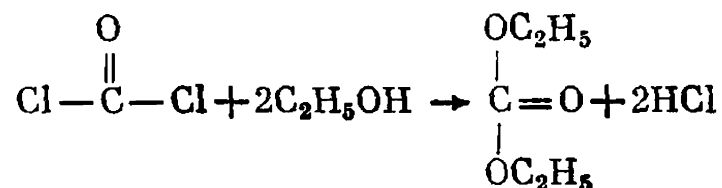
is oxidized by the phosgene (the oxidation products are insoluble and make the solution turbid).

Free chlorine can get into chloroform as a product of phosgene decomposition or in the electrolytic method of producing chloroform.

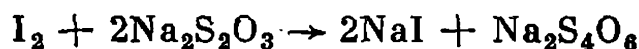
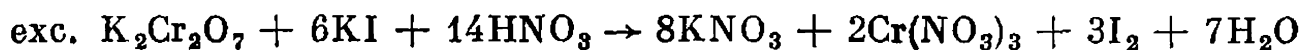
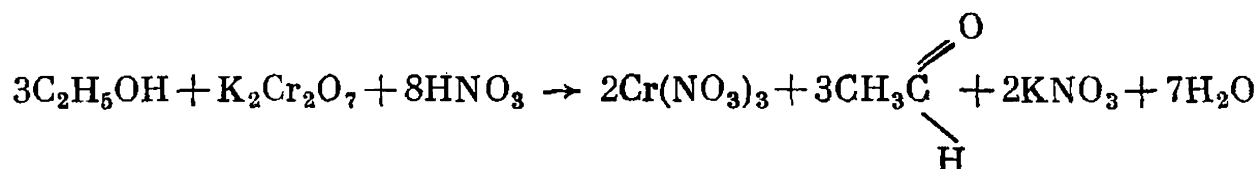
This admixture is detected by adding a potassium iodide solution, as a result of which molecular iodine evolves. It colours starch blue:



Ethanol is added to chloroform as a preservative in an amount from 0.6 to 1% of the mass of the chloroform. In the presence of ethanol, phosgene is decontaminated because diethyl carbonate (a harmless compound) forms:



This is why the State Pharmacopoeia requires not only the qualitative detection of the ethanol, but also its quantitative determination, which must not exceed 1% of the mass of the chloroform. For this purpose, an excess of a standard solution of potassium dichromate and nitric acid is added to a definite amount of the chloroform. The dichromate oxidizes the ethanol to acetaldehyde (the odour of fresh apples). The excess of the potassium dichromate is determined iodimetrically:



Thus, this reaction is simultaneously a qualitative test for ethanol and is used for its quantitative determination.

The tests for admixtures of aldehyde, phosgene, and other organic impurities in chloroform for narcosis must be conducted under definite conditions and with a prolonged time exposure as required by the State Pharmacopoeia.

Chloroform is a colourless, transparent, heavy, mobile liquid with a characteristic odour and a burning taste. It is quite volatile. It dissolves poorly in water, but mixes in all proportions with alcohol, petrol, and essential oils. Its boiling point is 59.5-62 °C. Its specific gravity is 1.474-1.483. Chloroform vapour does not ignite or explode.

The State Pharmacopoeia does not require the detection of the preparation by chemical reactions because the boiling point and specific gravity can be criteria for its identification. But a number of chemical reactions can nevertheless be conducted to confirm the presence of chloroform.

From the chemical standpoint, chloroform is trisubstituted methane. The chlorine in the chloroform molecule is bound to the car-

bon atom and is not ionogenic, therefore it can be detected using a silver nitrate solution only after decomposition of the molecule. This is achieved by reacting the chloroform with an alkali solution:



Chloroform enters into a number of reactions of the condensation type, namely, a colour reaction with resorcinol, a reaction with aniline (the formation of benzoisonitrile having a pungent smell), etc.

Chloroform is administered as an agent for inhalation narcosis. Its merits are its quick action and non-flammability. But at the same time, it has a comparatively high toxicity, which considerably restricts its use.

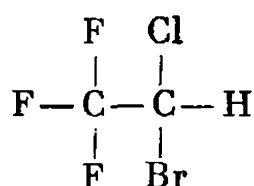
Chloroform is usually employed externally in a mixture with turpentine for massaging.

The liability of chloroform to become oxidized also determines the conditions for its storage. It must be stored with great care in orange glass carboys filled to the top and sealed, in a cool place. Chloroform for narcosis is dispensed in dark glass jars with a capacity of 50 ml, intended for a single use. Opened jars must never be used. After every six months, chloroform for narcosis must be subjected to a chemical analysis. It belongs to group B.

A more active agent for inhalation narcosis is ftorotan (halothane), which was synthesized in the USSR in 1960.

Ftorotan (*Phthorothanum*)

2-Bromo-2-chloro-1,1,1-trifluoroethane

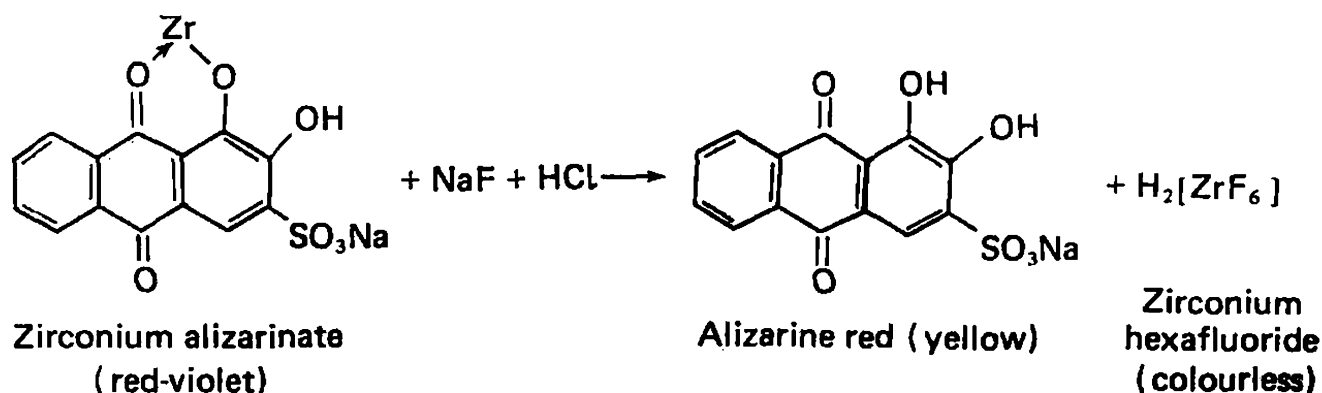


M.m. 197.39

Ftorotan (halothane) is a halogen derivative of ethane. It is a transparent, colourless, heavy, mobile, readily volatile liquid that smells like chloroform, and with a sweet and burning taste. It neither burns nor explodes, therefore it is absolutely safe in operations with the use of X-ray and electrical apparatus. Ftorotan dissolves only slightly in water, and mixes with anhydrous alcohol, ether, chloroform, trichloroethylene, and volatile and non-volatile oils.

Like other drugs used in inhalation narcosis, the criteria for the identification of ftorotan are its boiling point (49-51 °C), specific gravity, and refractive index. In addition, the State Pharmacopoeia recommends the detection of fluorine in a ftorotan molecule as an identification reaction.

For this purpose, the drug is mineralized (by fusing it with metallic sodium). The formed sodium fluoride NaF is detected with respect to the fluoride ion by reacting it with zirconium alizarinate (a complex of zirconium nitrate with alizarine red):



When a sodium fluoride solution (in an acidic medium) is added to zirconium alizarinate, the red-violet colour transforms into a yellow one owing to the decomposition of the zirconium alizarinate complex with the evolution of free alizarine red imparting the yellow colour to the solution.

The drug may contain admixtures of chlorides, bromides, free chlorine and bromine. They are detected by the relevant analytical reactions.

Ftorotan decomposes under the action of light, therefore it must be stored in dark glass bottles. To stabilize the drug, thymol is added to it (0.01 % of the mass of the drug).

The potency of ftorotan is two and four times greater than that of chloroform and ether, respectively. It has a comparatively low toxicity. It is used in various surgical operations, especially on thoracic organs, because it does not irritate the mucous membranes of the respiratory tract.

Ftorotan is used in a mixture with oxygen or in a mixture with nitrous oxide and oxygen, and also in the form of a mixture consisting of two parts of ftorotan and one part of ether. It is dispensed in dark glass bottles with a capacity of 50 and 250 ml. Like chloroform, it should be stored in a dry and cool place protected from the light.

Iodoform (*Iodoformium*)

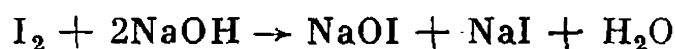
Triiodomethane

CHI₃

M.m. 393.73

Iodoform is used in medicine as an antiseptic. Unlike chloroform, the halogen here is not bound strongly and is easily detected with a silver nitrate solution. It is just this unstable bond of the halogen to the carbon atom that underlies the antiseptic effect of the drug.

The methods of preparation and raw materials for the synthesis of iodoform are the same as for chloroform. The only difference is that generally potassium or sodium hypoiodide (KOI or NaOI) is used as the oxidizing agent instead of chlorinated lime. These salts are unstable at ordinary temperatures, therefore they are prepared in the process of production in the reactor by the reaction of free iodine with a caustic alkali:



The process next follows the same scheme as for chloroform.

When iodine reacts with an alkali, sodium iodide evolves simultaneously with the hypoiodide. The sodium iodide is reacted with an oxidizing agent (NaOCl) to transform the iodide ion I^- into iodine I_2 . Thus, all the iodine is used to produce iodoform.

Iodoform can also be produced electrolytically, like chloroform.

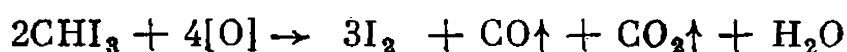
In its physical properties, iodoform is composed of lustrous flaked crystals of a lemon-yellow colour. Its melting point (with decomposition) is 116-120 °C. It has a pungent unpleasant and very lasting odour. It is virtually insoluble in water, sparingly soluble in alcohol, and more readily in boiling alcohol. It is soluble in ether and chloroform. It is volatile even at room temperature.

Iodoform solutions are very sensitive to light and air and easily decompose. When heated with concentrated sulphuric acid, violet iodine vapour evolves. This reaction is used to confirm the presence of the drug. The State Pharmacopoeia tolerates admixtures of chlorides and sulphates within the limits indicated by the standard. No admixtures of mineral salts and colouring substances are tolerated in the drug.

It is analysed quantitatively by argentometry. An exactly weighed specimen of the drug is dissolved in alcohol and an excess of a standard solution of silver nitrate and nitric acid is added. The mixture is heated on a water bath during 30 minutes while protecting the reaction flask from light. A silver iodide precipitate forms. The excess of the silver nitrate solution is titrated with ammonium thiocyanide (using ammonium iron alum as the indicator). The State Pharmacopoeia requires that the drug contain at least 99% of pure iodoform.

Iodoform is applied externally as an antiseptic in the form of powders, ointments, and wadding for surgical dressings of patients with infected wounds.

The physiological action of iodoform consists in that when it comes into contact with the wounded surface of a tissue, the oxidizing enzyme (catalase) of the blood or other fluid of the wounded tissue oxidizes the iodoform with the evolution of iodine, and the latter exhibits a disinfecting action:



Brown

This reaction proceeds gradually and very slowly, thus prolonging the antiseptic effect of the iodoform.

The drug should be stored in well closed jars of dark glass or ceramics in a cool place protected from light.

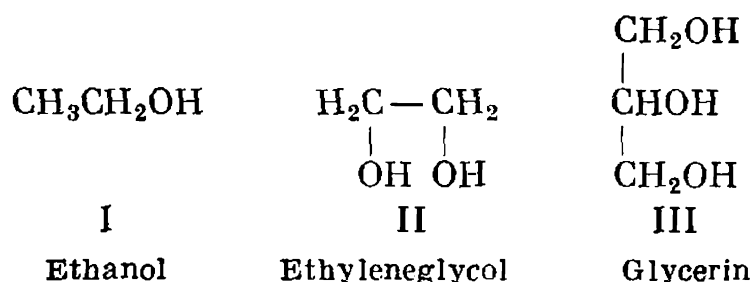
REVIEW QUESTIONS

1. What compounds are called the halogen derivatives of hydrocarbons?
2. How does the introduction of halogens into a molecule of an aliphatic hydrocarbon affect the pharmacological action of the substance?
3. What is the boiling point of ethyl chloride?
4. What is the application of ethyl chloride based on?
5. Can the presence of chlorine in ethyl chloride be proved if the latter is poured into water and a silver nitrate solution is added?
6. Why is chloroform for narcosis produced from chloral hydrate, and not from a cheaper substance such as chlorinated lime?
7. Why do chloroform molecules first have to be destroyed, and only then can the substance be analysed qualitatively and quantitatively?
8. What happens to chloroform when it is left in the light and in the air?
9. What requirements must the purity of chloroform meet and why?
10. What requirements must the storage of chloroform meet and what is this due to?
11. What process occurs when iodoform stands in the light?
12. What is the physiological action of iodoform based on? Explain it from a chemical viewpoint.
13. Compare the chemical structure of fluorotan (halothane) and chloroform and their pharmacological action.
14. Why does the purity of fluorotan have to be checked every six months?

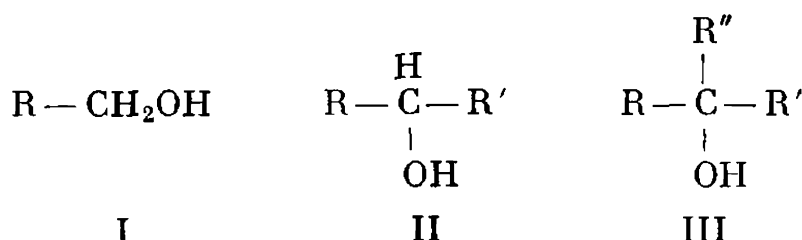
Chapter 12. Alcohols

Alcohols are derivatives of hydrocarbons in whose molecules one or more hydrogen atoms are substituted by hydroxyl groups. In the general form, an alcohol molecule can be represented as $R-OH$. Depending on the number of hydroxyl groups in an alcohol molecule, the molecular mass, the nature of the hydrocarbon radical to which the hydroxyl group is attached, and the nature of the parent hydrocarbon from which the alcohol molecule has been derived, alcohols differ somewhat in their physical and chemical properties. Alcohols are divided:

(1) into monatomic (I) and polyatomic (II and III) alcohols depending on the number of hydroxyl groups in a molecule:

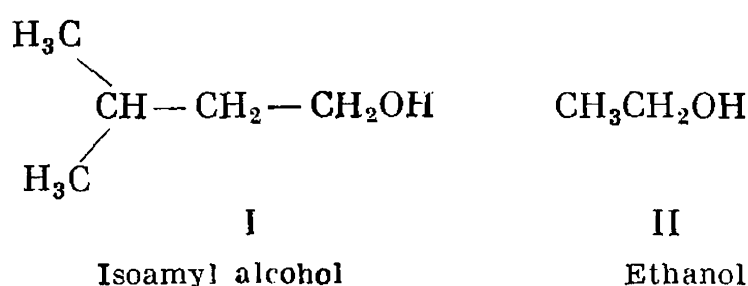


(2) into primary (I), secondary (II), and tertiary (III) alcohols depending on the nature of the carbon atom to which the hydroxyl group is attached:

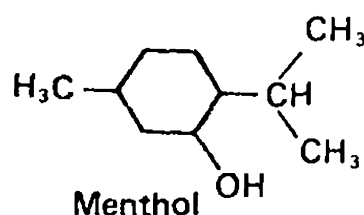


(3) depending on the nature of the parent hydrocarbon, into:

(a) aliphatic alcohols—the parent hydrocarbon is a branched (I) or unbranched (II) chain:



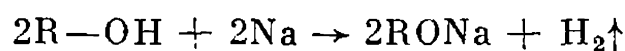
(b) cyclic alcohols—the hydroxyl group replaces a hydrogen atom in a cyclic hydrocarbon:



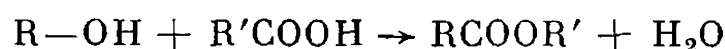
In all the above compounds, alcohol hydroxyl is the functional group, and it is exactly the latter group that underlies the physical, chemical, and pharmacological properties of the alcohols. For example, hydroxyl increases the solubility of a substance. The alcohols, especially the lower ones, dissolve in water. The solubility diminishes with a growth in the length of the carbon chain. Secondary alcohols are generally more soluble than primary ones, and tertiary alcohols are more soluble than secondary ones. This also relates to the boiling point: the latter lowers from primary alcohols to tertiary ones.

Polyatomic alcohols have a sweet taste; this property increases with a growth in the number of hydroxyl groups in an alcohol molecule.

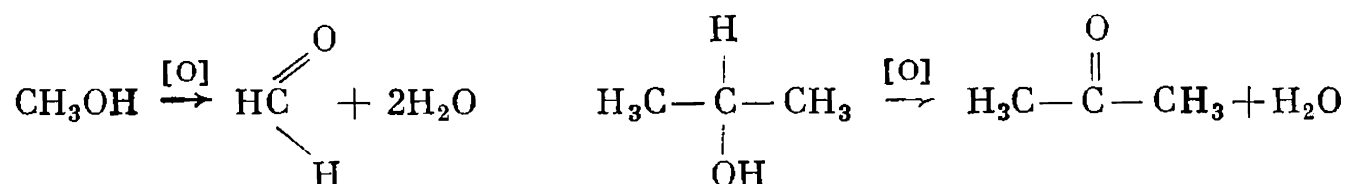
Alcohols have a neutral reaction and react with alkali metals with the evolution of hydrogen:



They form esters with acids:



Primary and secondary alcohols are easily oxidized. The oxidation of primary alcohols yields aldehydes, and of secondary ones—ketones:



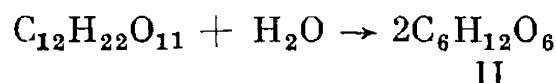
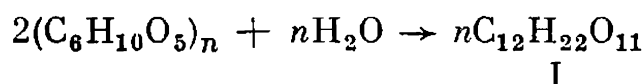
Tertiary alcohols are oxidized with great difficulty.

95% Ethyl Alcohol (*Spiritus aethylicus* 95%)

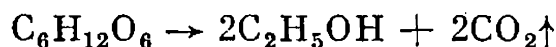
$\text{C}_2\text{H}_5\text{OH}$

M.m. 46.07

Ethyl alcohol or ethanol can be produced from natural compounds and synthetically. In the former case, it is produced by the fermentation of saccharine substances: polysaccharides are transformed by enzymes into maltose (I), which decomposes, in turn, into glucose (II):

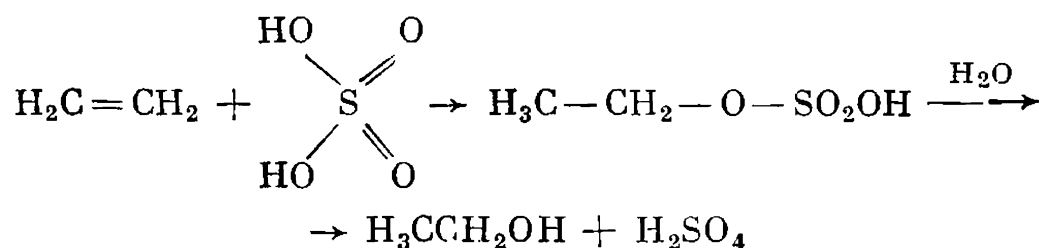


The product of glucose fermentation is alcohol (in pharmacological practice ethyl alcohol is usually called simply alcohol):

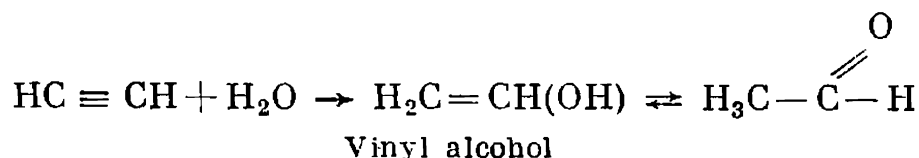


Ethyl alcohol can also be produced synthetically from unsaturated compounds:

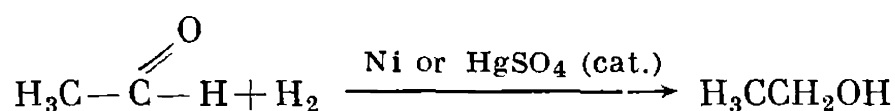
(1) from ethylene by reacting it with sulphuric acid; the latter combines with the ethylene to form ethyl hydrogen sulphate, which is decomposed by water into alcohol and sulphuric acid:



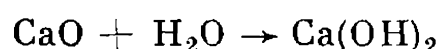
(2) from acetylene by the Kucherov reaction; this method consists in the catalytic hydrogenation of acetic aldehyde which is produced, in turn, from acetylene:



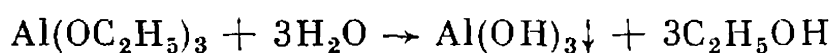
The acetic aldehyde is distilled and reduced by hydrogen in the presence of a catalyst (nickel, mercury sulphate, etc.), the product being ethyl alcohol:



Alcohol intended for medical purposes and produced in any of the above ways is thoroughly purified from possible admixtures by fractional distillation (rectification). The product is 95-96% alcohol. To obtain anhydrous (absolute) alcohol, chemical methods of binding the water are employed, for example by unslaked lime (calcium oxide) or anhydrous sodium sulphate:



A more up-to-date method for removing the water is the use of aluminium ethylate. It absorbs the water and transforms into aluminium hydroxide:



The State Pharmacopoeia describes the following ethyl alcohol preparations: 95%, 90%, 70%, and 40%.

Ethyl alcohol is a transparent liquid. It is volatile, readily ignites, has a characteristic odour and a burning taste. It burns with a bluish, slightly glowing flame. It mixes in all proportions with water, ether, chloroform, acetone, and glycerin.

The presence of alcohol is established by the following reactions:

(a) the formation of iodoform when it reacts with an iodine solution in an alkaline medium:

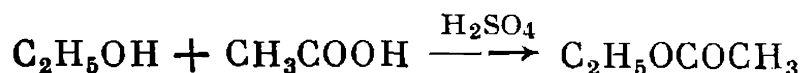


This reaction is sensitive, but it is insufficiently specific for alcohol, it also proceeds with compounds having in their molecule an ethoxy

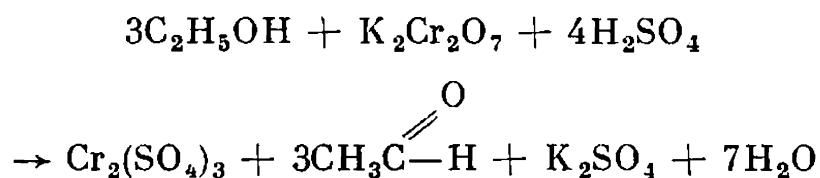
(OC₂H₅), aceto ($\text{CH}_3-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-$) or hydroxyethyl ($\text{CH}_3-\overset{\text{OH}}{\underset{\diagup}{\text{C}}}-$) group

such as acetone and lactic acid;

(b) a reaction of formation of esters with acids; when alcohol is reacted with glacial acetic acid in the presence of concentrated sulphuric acid, the product is ethyl acetate having a specific odour:



(c) the oxidation of alcohol by potassium bichromate in the presence of sulphuric acid with the formation of acetaldehyde having the odour of fresh apples:



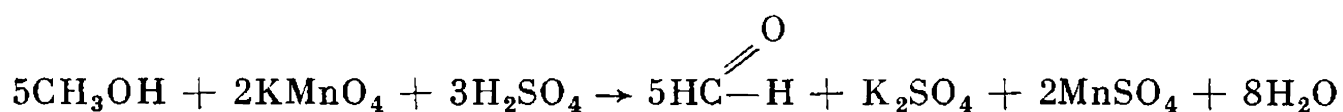
A typical property of alcohol is the magnitude of its specific gravity (or density). Depending on the alcohol concentration, the specific gravity varies, increasing when the concentration diminishes. The State Pharmacopoeia contains tables of the specific gravity of alcohol for various concentrations.

The impurities that may be present in ethyl alcohol are the products of its oxidation (acetaldehyde and acetic acid), dehydration products (unsaturated compounds having a reducing property), and residues of the synthesis raw materials and intermediates. For example, if ethyl alcohol was produced by the fermentation of saccharine substances, it can contain an admixture of fusel oils (a mixture of higher alcohols—butyl and isoamyl alcohols) that can be determined by their unpleasant smell.

“Hydrolysis” alcohol produced from sawdust can contain an admixture of methanol. This impurity cannot be tolerated because methanol is very poisonous and in a sufficient concentration may cause severe poisoning and blindness. Alcohol can contain an admixture of tanning substances if it was stored in oak kegs.

With a view to the possibility of the above impurities being contained in alcohol, the purity of ethyl alcohol used for medicinal purposes must meet definite requirements. The acidity of the alcohol is stipulated. It is proposed to conduct reactions of aldehyde detection with an ammonia solution of silver nitrate. The presence of reducing substances should be detected with a potassium permanganate solution which must not lose its colour during 20 minutes.

It is good practice to determine the presence of tanning substances by adding a small amount of an ammonia solution to a sample of the alcohol, and no colour should appear. A reaction for detecting an admixture of methyl alcohol must be conducted without fail. For this purpose, the common reaction for alcohols is employed—the oxidation of potassium permanganate in an acidic medium. In this case, both the ethanol and the admixture of methanol become oxidized. Oxidation of the latter produces formaldehyde:



The formaldehyde easily condenses with phenols and, particularly, with a phenolic (chromotropic) acid with the formation of a violet

condensation product. The acetaldehyde formed in the oxidation of the ethanol does not enter into this reaction because it has a very low ability of participating in a condensation reaction.

As regards its pharmacological properties, ethyl alcohol belongs to substances with a narcotic action. By acting on the cerebral cortex, it produces a typical alcoholic excitation, while in large doses it weakens the stimulating process in the cortex and suppresses the activity of the respiratory centre.

In concentrations of 50-70%, alcohol has good disinfecting properties and is used for disinfecting hands and surgical instruments.

In medicinal practice, alcohol is generally used as an external antiseptic and irritant for massages and compresses. Ethyl alcohol in various dilutions is used for the preparation of tinctures, extracts, and a number of medicinal agents administered externally. Alcohol, in addition, is widely used in chemical practice as a solvent. It is the main raw material in a number of chemical manufacturing processes such as the production of vinegar, chloroform, iodoform, various ethers and esters.

It should be stored in well closed glass bottles in a cool place.

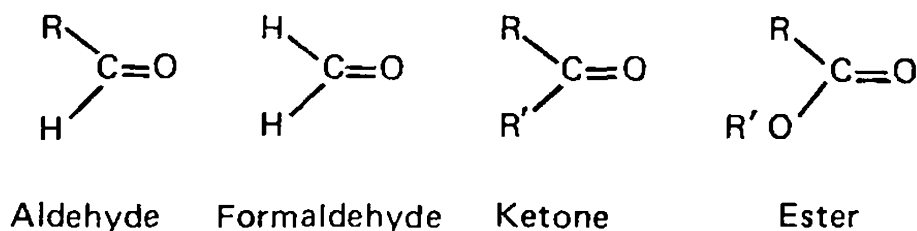
REVIEW QUESTIONS

1. How do the physical and chemical properties of alcohols change depending on the number of hydroxyl groups in a molecule?
2. How does the number of hydroxyl groups affect the solubility of alcohols in water?
3. How is the physiological activity of an alcohol affected by the length of the carbon chain, branching of the carbon chain, the position of the hydroxyl group in the molecule, the presence of an unsaturated bond in the molecule, and by the introduction of halogens into the molecule?
4. What properties of ethyl alcohol are used in the reactions of its identification?

Chapter 13. Aldehydes

The functional group of an aldehyde molecule that determines its reactivity is the carbonyl group ($>\text{C}=\text{O}$). This group is also present in molecules of ketones and esters.

The carbonyl carbon atom bound to hydrogen forms an aldehyde group ($-\overset{\text{O}}{\underset{\text{H}}{\text{C}}}-$):



An exception here is formaldehyde, in whose molecule the carbonyl carbon atom is bound to two hydrogens.

In ketones, two alkyl groups (R and R') are bound to the carbonyl carbon, and in esters, one alkyl group (R) and one alkoxy group (R'O—). All these types of compounds containing the same functional group thus have common properties and identification reactions.

In turn, each of these compounds also has particular, specific identification reactions distinguishing them from one another.

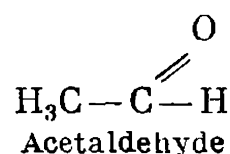
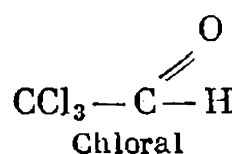
The physiological action of drugs containing an aldehyde group in their molecule varies and depends chiefly on the nature of the alkyl radical bound to the carbonyl carbon (Table 1).

TABLE 1. Drugs Containing an Aldehyde Group in Their Molecule and Their Main Action on an Organism

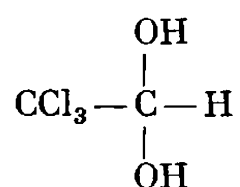
Formula	Name	Action on organism
$\begin{array}{c} \text{O} \\ \parallel \\ \text{H}-\text{C}-\text{H} \end{array}$	Solution of formaldehyde (formalin)	Antiseptic
$\begin{array}{c} \text{OH} \\ \diagup \\ \text{CCl}_3-\text{CH} \\ \diagdown \\ \text{OH} \end{array}$	Chloral hydrate	Sedative, anti-convulsive
$\text{CH}_2\text{OH}-[\text{CHOH}]_4-\begin{array}{c} \text{O} \\ \parallel \\ \text{C}-\text{H} \end{array}$	Glucose	Roborand
$\begin{array}{c} \text{O} \\ \parallel \\ (\text{CH}_3)_2\text{C}=\text{CH}-(\text{CH}_2)_2-\text{C}=\text{CH}-\text{C}-\text{H} \\ \mid \\ \text{CH}_3 \end{array}$	Citral	Lowers arterial blood pressure
$\begin{array}{c} \text{O}_2\text{N}-\text{C}_6\text{H}_4-\text{C}(\text{Cl})=\text{CH}-\begin{array}{c} \text{O} \\ \parallel \\ \text{C}-\text{H} \end{array} \end{array}$	Cyminal	Antimicrobial agent

An increase in the length of the alkyl radical in an aldehyde molecule amplifies its physiological activity, but its toxicity also grows.

The introduction of a halogen into an aldehyde molecule increases its narcotic (sedative) action. The narcotic properties of chloral are more pronounced than those of acetaldehyde:



An aldehyde group increases the toxicity of a substance, but it can be lowered substantially by the formation of the hydrate form of the aldehyde. Only a chlorinated aldehyde can form a hydrate. The hydrate form of chloral has a low toxicity and is used in medicine under the name of chloral hydrate exhibiting a sedative action:



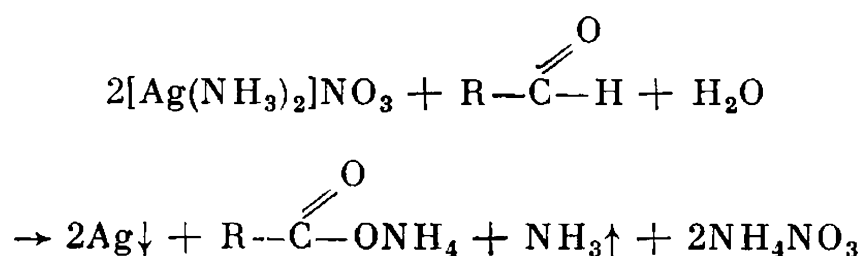
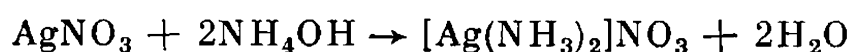
As regards their physical properties, aldehydes can be gaseous (formaldehyde), liquid (the lower aldehydes), and insoluble solid (the higher aldehydes) substances. Aldehydes dissolve well in alcohol and ether. The lower aldehydes have an unpleasant stifling smell. Aldehydes with a high molecular mass have a pleasant odour of flowers.

In the chemical respect, aldehydes are very reactive compounds. This is due to the presence in their molecule of a highly polarized double bond which is responsible for the chemical properties of the aldehydes. Many reactions characteristic of aldehydes such as the formation of oximes and semicarbazones are employed for the qualitative and quantitative analysis of drugs of the aldehyde group.

Among the chemical properties of aldehydes utilized in the reactions of their identification, the following must be noted:

1. Aldehydes are readily oxidized, being good reducing agents themselves. The reducing ability of aldehydes is illustrated by the following reactions:

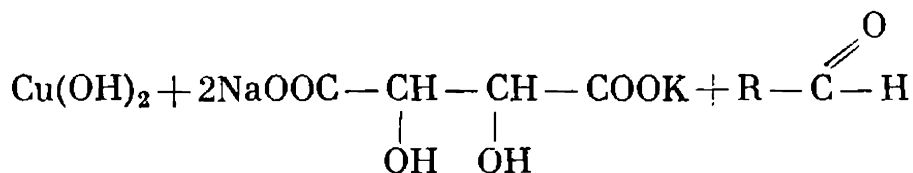
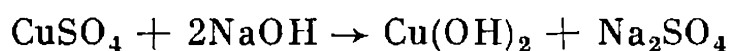
(a) a reaction with an ammonia solution of silver nitrate (the formation of a silver mirror); when an aldehyde solution is added to an ammonia solution of silver nitrate with heating, a deposit of reduced silver in the form of a mirror forms on the walls of the test tube:



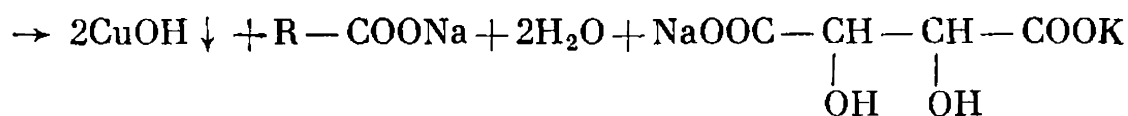
This reaction is recommended by the State Pharmacopoeia for identifying drugs with an aldehyde group in their molecule;

(b) a reaction with Fehling's solution; the latter is added to a solution of the aldehyde being tested and the mixture is heated. A brick-

red precipitate of copper(I) oxide Cu_2O gradually forms:

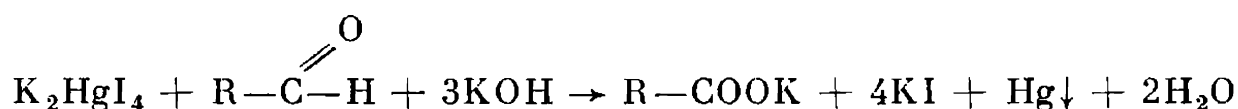


Fehling's solution



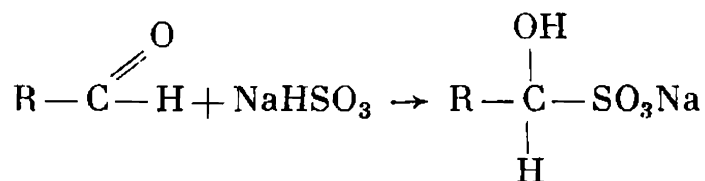
Brick-red

(c) a reaction with Nessler's reagent in an alkaline medium; reduced mercury having a dark colour precipitates:

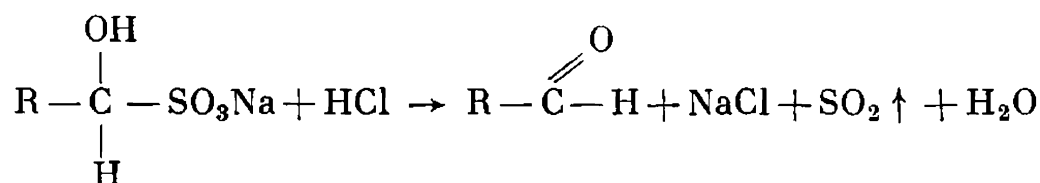


When employing these reactions in pharmaceutical analysis, one has to take their sensitivity into consideration. To identify a drug containing an aldehyde group, one should use the reaction with silver nitrate or Fehling's solution, while to detect aldehydes as impurities in drugs, a more sensitive reaction is needed (with Nessler's reagent).

2. Addition reactions of aldehydes are of interest for pharmaceutical analysis because their products are characterized by a definite melting point for each aldehyde. For example, aldehydes readily combine with sodium hydrogen sulphite to form bisulphite derivatives of the aldehydes—crystalline substances having a definite melting point:



The bisulphite derivatives of aldehydes when heated with dilute acids produce the relevant aldehyde and sulphurous acid (the latter decomposes into sulphur dioxide and water):

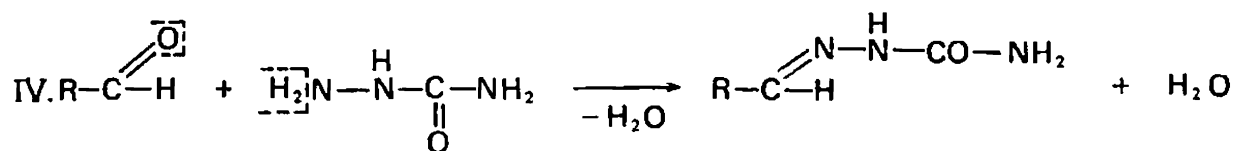
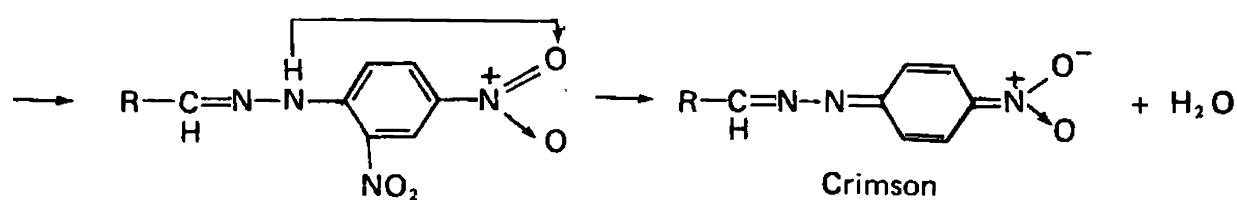
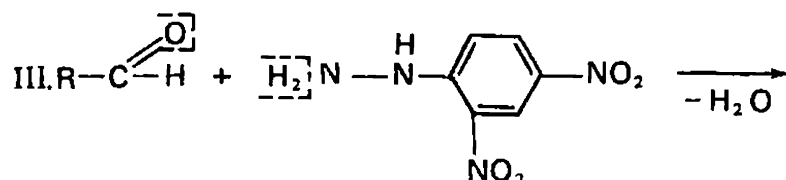
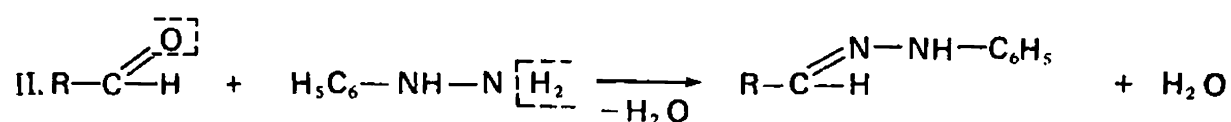
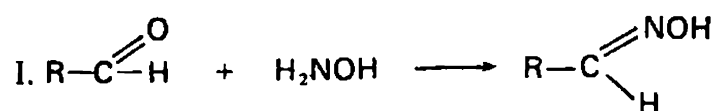


This reaction is used not only to identify a drug containing an aldehyde group, but also to purify aldehydes and separate them from

mixtures with other substances that fail to react with sodium hydrogen sulphite.

Addition reactions also include reactions of aldehydes with fuch-sinesulphurous acid*, when the solution acquires a red or red-violet colour. The addition of a mineral acid to the reaction mixture causes the colour to vanish. The only exception is formaldehyde in whose presence the colour does not vanish. Hence, this reaction is considered to be specific for formaldehyde.

3. Substitution reactions are reactions of aldehydes with amines and their derivatives, for example with hydroxylamine (I), phenylhydrazine (II), 2,4-dinitrophenylhydrazine (III), and semicarbazide (IV):

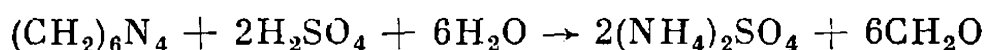


The products of the reaction between these substances and aldehydes precipitate and after drying have a definite melting point or colour (2,4-dinitrophenylhydrazine), therefore these reactions are used for identifying drugs containing an aldehyde group.

The pharmacopoeial drugs of the aldehyde group include a formaldehyde solution (formalin), chloral hydrate, and glucose.

* Fuch-sinesulphurous acid is prepared by passing sulphur dioxide through a fuchsine solution and is a colourless liquid.

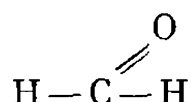
In this group of drugs, we shall also consider hexamethylenetetramine (methenamine) whose physiological action is due to the formaldehyde evolving when it reacts with an acid:



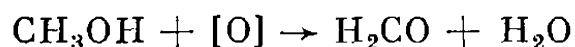
Solution of Formaldehyde. Formalin (*Solutio Formaldehydi*)

CH_2O

M.m. 30.03



Formaldehyde is produced in the industry by oxidizing methanol. A stream of air is passed through methanol heated to 50°C , becomes saturated with methanol vapour, and is fed into a tube with a red-hot copper coil (the copper plays the role of a catalyst):

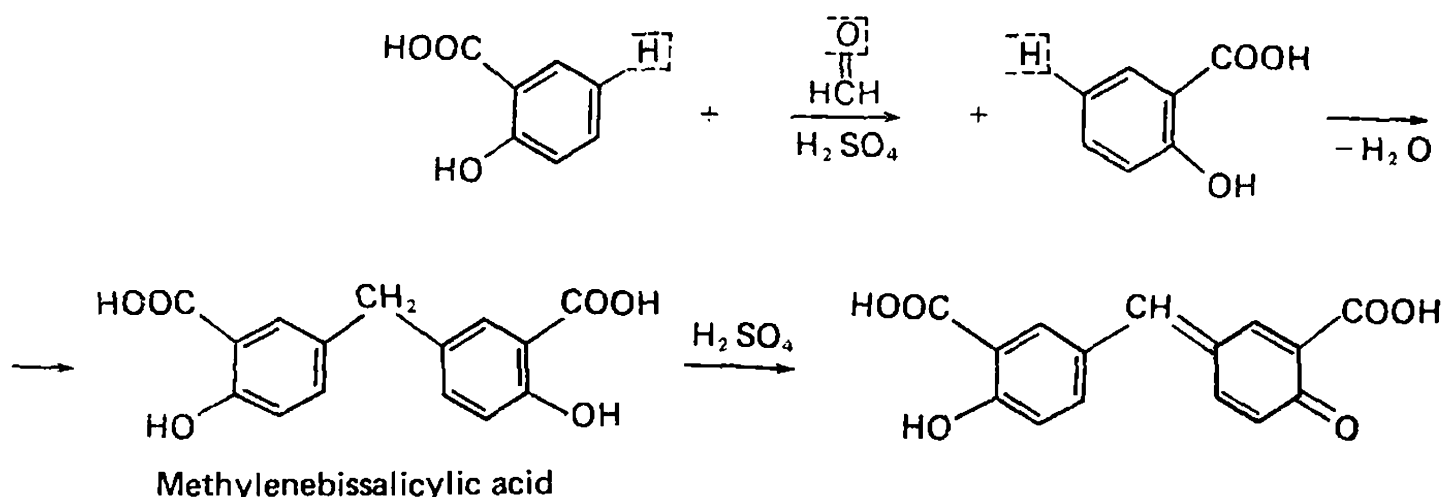


Formaldehyde is a gas with a pungent unpleasant odour, soluble in water. It mixes in all proportions with water and alcohol. A 40% aqueous solution of formaldehyde (*Solutio Formaldehydi*) called formalin is a pharmacopoeial preparation. It is a transparent colourless liquid with a pungent peculiar odour.

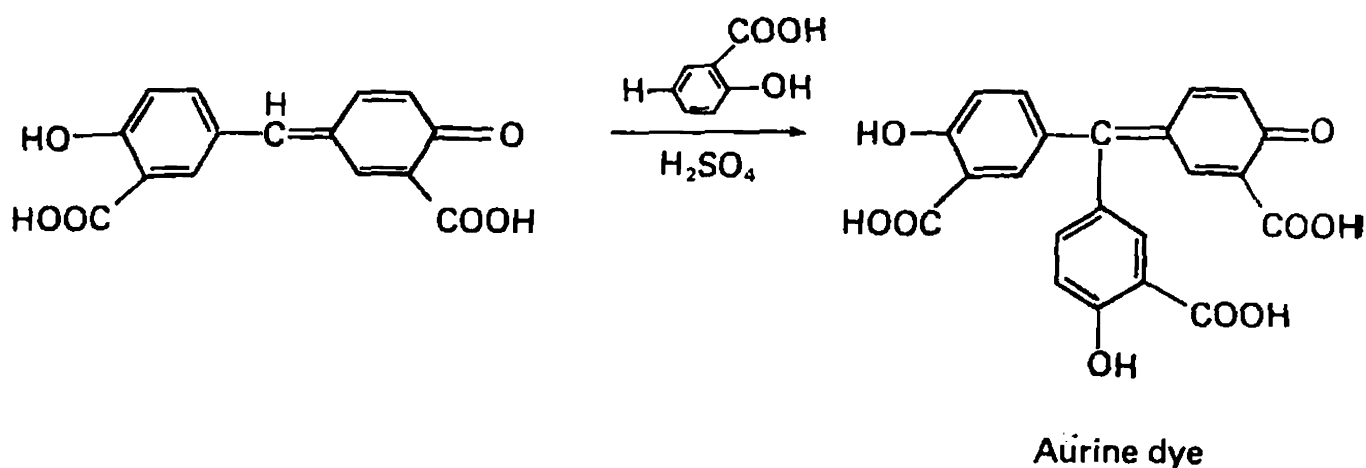
To identify the preparation, one can use all the general reactions characteristic of aldehydes (see above), but specific reactions exist for formaldehyde that distinguish it from other aldehydes. Such reactions include the reaction of formaldehyde with phenols in the presence of concentrated sulphuric acid with the formation of coloured products.

The State Pharmacopoeia recommends phenolic acids for this purpose, namely, salicylic or chromotropic acid.

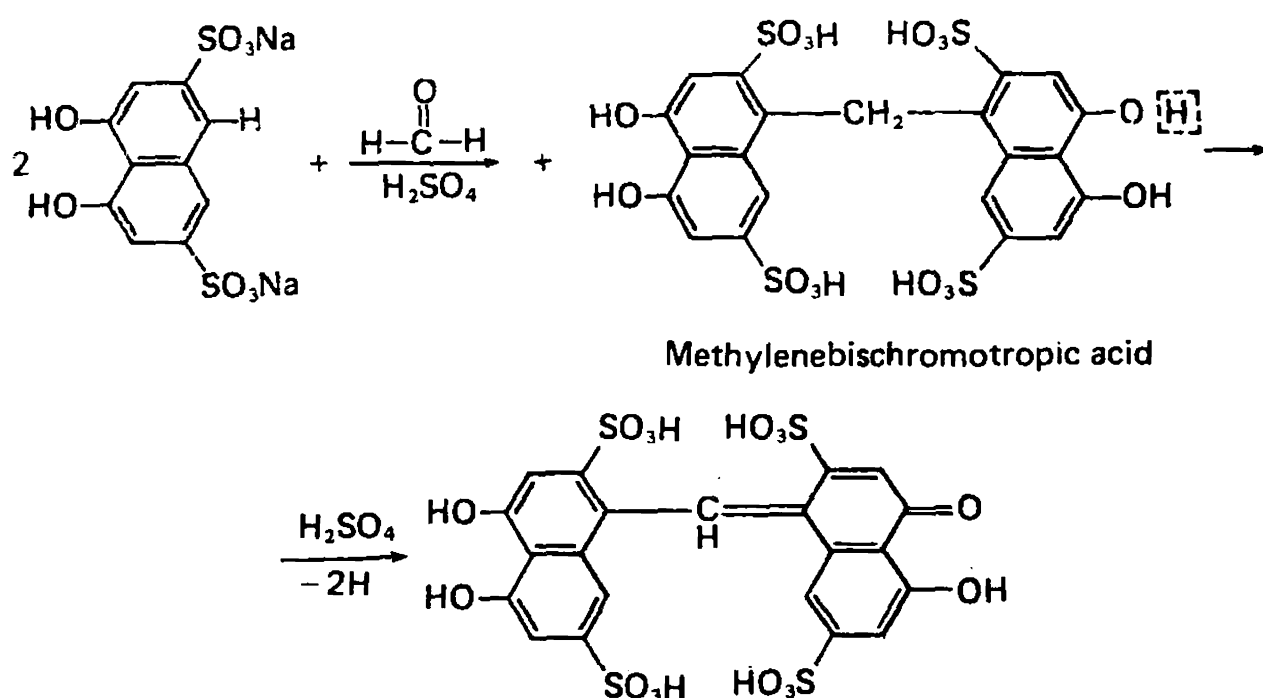
Reaction with salicylic acid:



In the first stage of the reaction, the concentrated sulphuric acid plays the role of a dehydrating agent, and therefore the phenol condenses with the formaldehyde to form methylenebissalicylic acid, which is oxidized by the sulphuric acid to a quinoid structure. The latter reacts with the salicylic acid remaining unreacted. In the presence of sulphuric acid, oxidation occurs with the formation of a red aurine dye:



The reaction with chromotropic acid proceeds similarly:

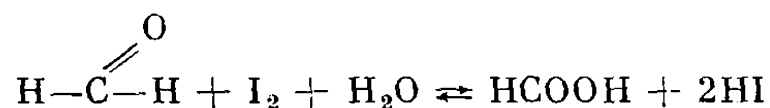


At a low temperature (below 9 °C), formaldehyde readily polymerizes and forms paraform $(\text{CH}_2\text{O})_n$ that separates as a white precipitate. Paraform does not have the properties inherent in a formaldehyde solution as a medicinal preparation. Therefore a formaldehyde solution should never be stored at a temperature below 9 °C.

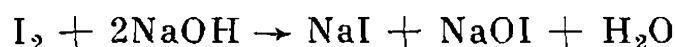
A formaldehyde solution may contain an admixture of formic acid that can form in the production of the formaldehyde. Therefore, the State Pharmacopoeia tolerates a certain acidity of the preparation.

To prevent any possible oxidation-reduction processes and to stabilize the preparation, methanol (not over 1%) is added to it.

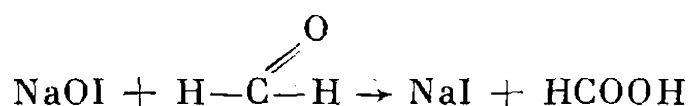
The quantitative determination of the preparation is based on the ability of the aldehyde to become oxidized. Iodine, hydrogen peroxide, or Nessler's reagent can be used as the oxidizing agent. The State Pharmacopoeia recommends the iodimetric method of determining formaldehyde in which the latter is oxidized by iodine:



Since the reaction is reversible, the acid formed must be neutralized with an alkali. But the iodine also reacts with an alkali to form a hypoiodite and an iodide:



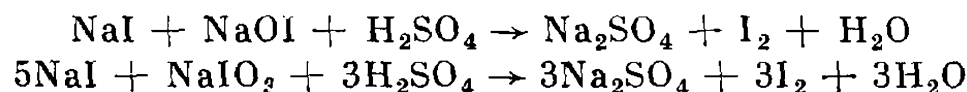
The hypoiodite can oxidize the formaldehyde:



When the hypoiodite is left standing, it transforms into the iodate:

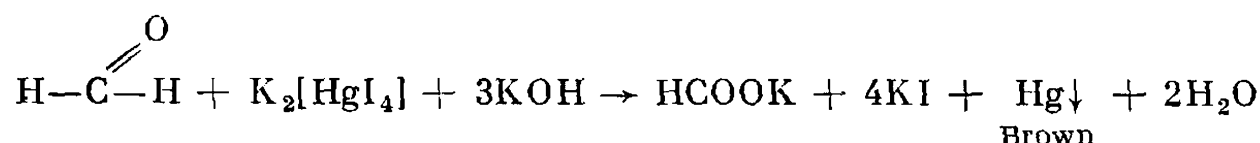


After the formaldehyde has become oxidized, sulphuric acid is added, which displaces the iodine from the remaining salts (NaOI and NaIO₃) and from an amount of sodium iodide equivalent to them:

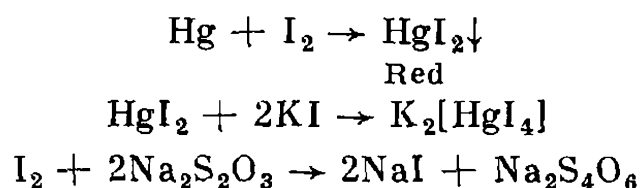


The evolved iodine is titrated with sodium thiosulphate. The difference between the amount of iodine and the sodium thiosulphate spent for titration of the iodine equals the amount of iodine spent for oxidation of the formaldehyde. This method is suitable if the formaldehyde solution contains no admixtures of other aldehydes and acetone, which also react with iodine.

A different method can be used to determine formaldehyde in which Nessler's reagent is used as the oxidizing agent:



Next an excess of a standard iodine solution is added to bind the mercury, and the excess iodine is titrated with sodium thiosulphate:

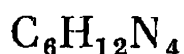
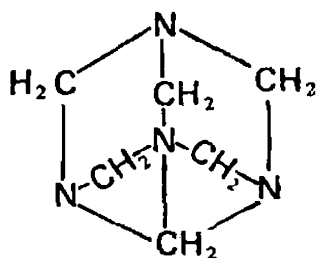


A formaldehyde solution (formalin) is used in medicine as a disinfectant. Its action is based on its ability to coagulate a protein. The proteins of bacteria coagulate under the influence of formaldehyde, which destroys the bacteria. A formaldehyde solution is a protoplasmic poison and cannot be prescribed for oral administration. It is used as a disinfectant by surgeons for washing their hands and treating surgical instruments (a 0.5% solution), washing feet disposed to sweating (a 0.5-1% solution), and for syringing in a dilution of 1:1000-1:3000.

Since a formaldehyde solution can impart elasticity to tissues, it is often used for preserving anatomical and biological preparations.

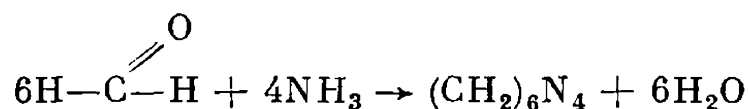
Formaldehyde must be stored in a dark place in well closed bottles or carboys at a temperature not below 9 °C. The carboys must have a label warning about the poisonous nature of the formaldehyde solution.

Hexamethylenetetramine (*Hexamethylenetetraminum*)



M.m. 140.19

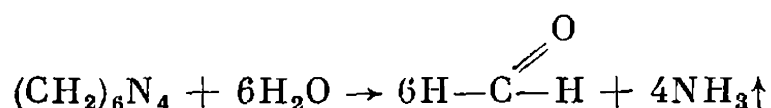
Hexamethylenetetramine (methenamine, urotropin, hexamine) is produced by reacting a formaldehyde solution with ammonia. It was first prepared by A. Butlerov (1860), but only 35 years after its discovery was it first used in medicine. The raw materials used for its production are 40% aqueous formaldehyde and ammonia water. The 25% ammonia water is added to the formaldehyde solution, the mixture is stirred, and the temperature is maintained at 40-50 °C:



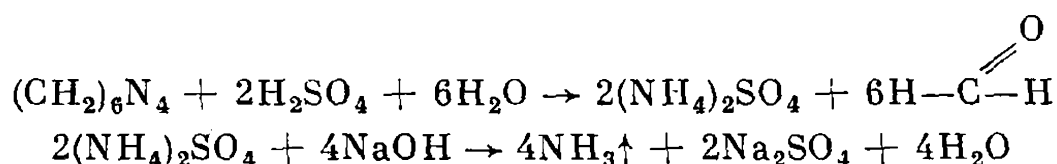
After completion of the reaction, the medium of the reaction mixture should be alkaline and there should be a smell of ammonia. Activated carbon is added to the mixture, the latter is filtered, and the filtrate is evaporated in vacuum until a pasty mass forms. Cooling yields crystals of hexamethylenetetramine. They are sucked out, rinsed, and dried at 30-35 °C. The obtained preparation is recrystallized from alcohol.

Hexamethylenetetramine is an odourless white crystalline powder, very hygroscopic. It has a burning taste, first sweet, and then bitterish. The drug dissolves well in water and alcohol, is soluble in chloroform, and almost insoluble in ether. Aqueous solutions of hexame-

thylenetetramine have a weakly alkaline reaction. When heated, the crystals sublime without melting. When aqueous solutions of hexamethylenetetramine are heated, hydrolysis occurs with the formation of formaldehyde and ammonia:



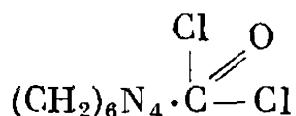
In an acidic medium, hexamethylenetetramine decomposes with the evolution of formaldehyde. When a solution of an alkali is added to the reaction mixture, a smell of ammonia is felt:



This reaction is recommended by the State Pharmacopoeia to identify hexamethylenetetramine.

When it is heated with salicylic acid in the presence of concentrated sulphuric acid, a violet-red colour appears. The reaction is based on the evolution of formaldehyde, which forms an aurine dye with salicylic acid in the presence of sulphuric acid (see the reactions for identifying *Solutio Formaldehydi*).

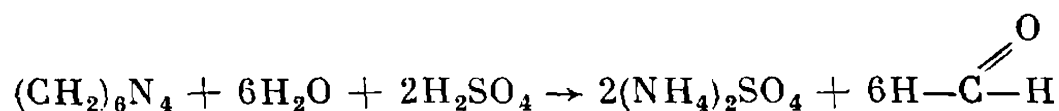
Hexamethylenetetramine is a monoacidic base; the tertiary nitrogen imparts basic properties to it, therefore it forms double salts with acids, for example, hexamethylenetetramine hydrochloride $(\text{CH}_2)_6\text{N}_4 \cdot \text{HCl}$. The presence of tertiary nitrogen, as in alkaloids, also underlies the formation of picrates (a yellow precipitate), tetraiodides $(\text{CH}_2)_6\text{N}_4 \cdot \text{I}_4$, and other reaction products. Hexamethylenetetramine can form complexes with salts of silver, calcium, and with phosgene:



As regards the quality of the drug, the State Pharmacopoeia does not tolerate organic admixtures and admixtures of ammonium salts (no yellow colour should appear when Nessler's reagent is added to a solution of the drug with heating) and of paraform (turbidity of the solution when Nessler's reagent is added with heating). Admixtures of chlorides, sulphates, and heavy metals are tolerated within the limits set by the relevant standards.

The content of the drug can be determined by neutralization. A weighed sample of the drug is dissolved with heating in a definite amount of a standard sulphuric acid solution. After the mixture cools, the excess acid is titrated with an alkali using methyl red as an indi-

cator. A control test is conducted simultaneously under the same conditions (the official method):



Hexamethylenetetramine as a base can be titrated with an acid using a mixed indicator (methylene blue and methyl orange) until the colour changes from green to blue-violet. This method is less accurate than the first one, but it is employed quite often in the express analysis of drug mixtures.

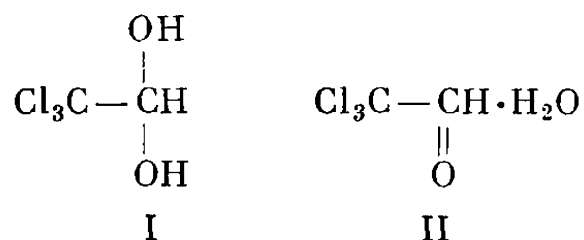
Hexamethylenetetramine is used as a disinfectant. Its action is based on the formation of formaldehyde in an acidic medium, which is just what exhibits a disinfecting action. It is administered to treat diseases of the urinary tracts. It must be taken into account that if the urine does not have an acidic reaction, the drug is not effective because it does not decompose into formaldehyde and other products. In addition to its antiseptic action, hexamethylenetetramine exhibits an antipodagric effect, hence it is also administered to patients suffering from rheumatism.

Hexamethylenetetramine is also widely used as an anti-influenza agent. It is administered orally in powders and tablets and intravenously in the form of a 40% solution.

It is dispensed in 0.25- and 0.5-g powders and tablets, and also in ampoules containing 5-10 ml of a 40% solution. It should be kept in well closed jars.

Chloral Hydrate (*Chloralum hydratum*)

(A Problem Solving Research Method)



Give the chemical name of the preparation of formula I. Characterize the chemical structure of the preparation of formula II. What functional group is characteristic of chloral hydrate? What class of compounds does chloral hydrate relate to?

Synthesize chloral hydrate.

Use samples of the preparation to study its physical properties, namely, the colour and odour of the crystals.

Chloral hydrate is hygroscopic at an increased humidity. It slowly volatilizes in the air.

Put 0.1 g of chloral hydrate into each of two test tubes, add 2 ml of water to the first and 1 ml of alcohol to the second tube. Make conclusions on the solubility of chloral hydrate.

Perform an identification test.

1. To 0.2 g of chloral hydrate add 1 ml of a 1 *N* sodium hydroxide solution. See what happens and compile the equation of the reaction.

2. Dissolve 0.2 g of chloral hydrate in 2 ml of water, add 1 ml of an ammonia solution of silver oxide and slightly heat the mixture. Observe what happens and compile the equation of the reaction. Which functional group is responsible for this reaction? Explain the chemical meaning of the reaction.

Perform a quantitative determination.

Dissolve 0.1 g of chloral hydrate in 10 ml of a 0.1 *N* sodium hydroxide solution (add it from a burette). In five minutes, titrate the excess sodium hydroxide with a 0.1 *N* hydrochloric acid solution (take two drops of phenolphthalein as the indicator) until the colour vanishes.

Name the method of quantitative determination. Write the equations of the reactions. Perform the required calculations. Conclude whether the preparation corresponds to the requirements of the pharmacopoeia. The State Pharmacopoeia stipulates that the preparation must contain at least 99% and at most 101% of chloral hydrate.

Storage conditions. Group B.

What other conditions are required for the storage of chloral hydrate?

The maximum single dose is 2.0 g, the maximum daily dose is 6.0 g.

What is the drug used for?

Upon completion of their independent work, the students discuss all the questions at the blackboard.

REVIEW QUESTIONS

1. What functional group is characteristic of an aldehyde molecule?
2. How does lengthening of the alkyl radical affect the physiological activity of aldehydes?
3. What explains the high reactivity of aldehydes?
4. What chemical properties do aldehydes have?
5. What explains the widespread use of addition reactions for aldehydes?
6. Why is the ability of the aldehydes to participate in polymerization and condensation reactions studied by pharmaceutical chemistry?
7. What chemical property of formaldehyde is its reaction with salicylic acid based on?
8. Why can formaldehyde give a reaction of silver mirror formation?
9. What property of formaldehyde is the quantitative determination of its solution based on?
10. What are the requirements to the storage of formalin?

11. What will happen to a formaldehyde solution when it is kept at a temperature below 9°C?
12. May polymerized formalin be used in medicine?
13. Why must an aqueous solution of formaldehyde (formalin) never be taken orally?
14. Which properties of hexamethylenetetramine are used in its quantitative determination by neutralization, by argentometry, and by iodimetry?
15. Can solutions of hexamethylenetetramine be sterilized?

PRACTICAL LESSON

Analysis of Hexamethylenetetramine (Methenamine)

1. Perform identification reactions.

Heat an aqueous solution of the drug in a proportion of 1:10 with dilute sulphuric acid. A smell of formaldehyde is felt. Next add an excess of a sodium hydroxide solution and again heat the mixture; a smell of ammonia is felt. Write the equations of the chemical reactions.

2. Conduct a quantitative determination (the neutralization method by direct titration; express analysis).

Dissolve 0.1 g of the drug in 10 ml of water, add three drops of methyl orange and four drops of methylene blue and titrate with a 0.1 *N* solution of hydrochloric acid until a violet colour appears. Write the equation of the chemical reaction.

3. Calculate the content of hexamethylenetetramine in per cent in the drug by formula (1.1):

$$X = \frac{VKT}{a} \times 100 = \frac{VK \times 0.014}{0.1} \times 100$$

where *V* is the volume of the 0.1 *N* solution of hydrochloric acid, ml, *T* = 0.014 g/ml, and *a* is the mass of the sample taken for the determination, g.

The State Pharmacopoeia stipulates that the content of C₆H₁₂N₄ be at least 99%.

4. Conclude whether analysis has indeed confirmed hexamethylenetetramine and whether its content corresponds to the State Pharmacopoeia.

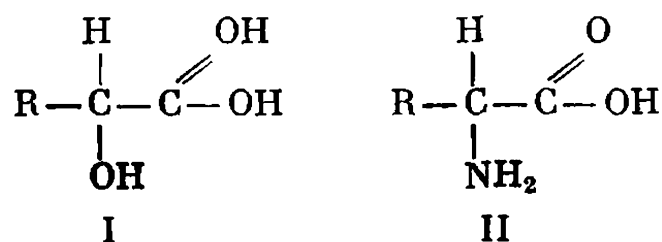
5. Are other methods of the quantitative determination of hexamethylenetetramine possible? Write the equations of the chemical reactions.

Chapter 14. Carboxylic Acids of the Aliphatic Series and Their Derivatives

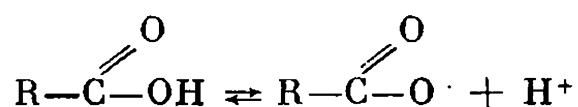
The carboxylic acids of the aliphatic series contain a carboxyl group in their molecule. In the general form, they can be depicted by the

formula $\text{R}-\overset{\text{O}}{\underset{\text{OH}}{\text{C}}}$. In addition to the carboxyl group, molecules of carboxylic acids can contain other functional groups such as the

hydroxyl group (hydroxycarboxylic acids) (I) or an amino group (amino acids) (II):



Free carboxylic acids are used very rarely in medicine. The explanation is that the acids dissociate into ions and ionogenic hydrogen:



It causes an irritating action and the higher the strength of an acid, i.e. the larger the degree of its dissociation, the more does it exhibit an irritating, cauterizing effect.

This is why not the acids themselves, but their salts and esters are used in medicine because the substitution of the carboxyl group hydrogen by a metal or an alcohol residue substantially reduces or completely eliminates the irritating action.

The degree of dissociation depends on the size and nature of the radical bound to the carboxyl group. With a growth in the molecular mass, the dissociation constant drops, which is also due to the fact that the solubility diminishes with a growth in the radical.

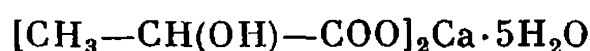
The pharmacological preparations of the carboxylic acids include potassium acetate, calcium lactate, sodium hydrogen citrate for injections, sodium citrate for injections, and calcium gluconate. The physiological action of these preparations is mainly due to the cation.

For example, potassium acetate is administered in cardiac oedema and as a salt diuretic; calcium lactate and calcium gluconate have an action like that of calcium chloride; sodium citrate provides an alkali reserve in the blood.

The chemical properties of the carboxylic acids are mainly determined by the properties of the carboxyl group.

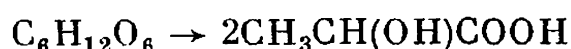
The carboxylic acids dissolve in caustic and carbonate alkalies with the formation of salts. They form variously coloured precipitates with salts of the heavy metals in a neutral medium. With alcohols, they form esters having a characteristic odour. All these properties of the carboxylic acids are employed in the pharmaceutical analysis of the relevant drugs. Since salts of carboxylic acids are used in medicine, they are identified according to the cation and anion.

Calcium Lactate (*Calcii lactas*)



M.m. 308.30

Calcium lactate is obtained in the industrial production of lactic acid. The latter forms in the fermentation of saccharine substances such as glucose:

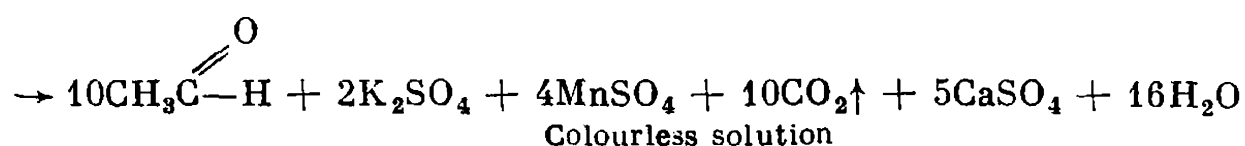
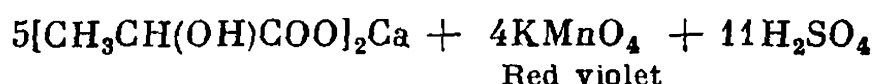


To produce calcium lactate, lactic acid is neutralized with calcium carbonate:



Calcium lactate is a fine white powder. Owing to the presence of crystallization water in the drug, it rapidly weathers in the air. It dissolves slowly in water with the formation of turbid solutions. It dissolves readily in hot water, and very poorly in alcohol, ether, and chloroform.

The drug is analysed for both the cation Ca^{2+} (see the reactions of identification of calcium chloride, p. 114f) and the anion (lactate ion). The latter is determined by the action of an oxidizing agent—a solution of potassium permanganate in an acidic medium. Under these conditions, the lactate ion evolves acetaldehyde, which is detected by its odour, while the solution is decolourized because of the reduction of the Mn^{7+} to Mn^{2+} :



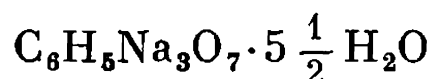
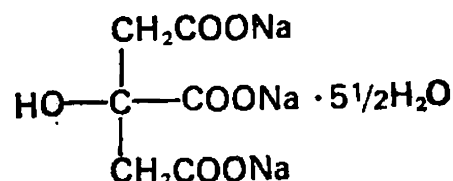
The State Pharmacopoeia does not tolerate any admixture of arsenic in the drug and establishes the limit of the alkalinity and acidity.

The content of calcium lactate in the drug is determined by complexometry (the pharmacopoeial method). A solution of the drug is titrated with Na-EDTA in the presence of an ammonia buffer solution using Acid Chrom Dark Blue as the indicator up to a blue-violet colour (see Sec. 1.1).

Calcium lactate is used in the same cases as calcium chloride. It is more favourable than the latter because it does not irritate the mucous membrane of the stomach. It is taken orally in the form of a powder (0.5–1 g) and intravenously in the form of 5–10% aqueous solutions (the drug is dissolved in hot water).

It is kept in well closed glass jars or in packages made from kraft paper with a semi-parchment lining.

Sodium Citrate for Injections (*Natrii citras pro injectionibus*)

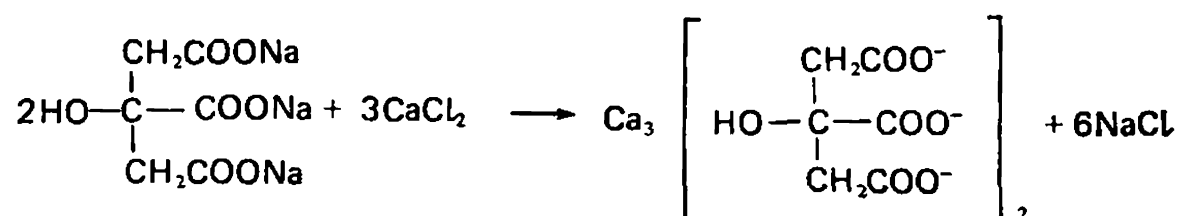


M.m. 357.16

In its chemical structure, the drug is the hydrate of the trisodium salt of citric acid. It is a white crystalline powder or colourless crystals with a salty taste. It dissolves well in water and weathers in the air.

Sodium citrate is prepared by neutralizing citric acid with an accurately calculated amount of sodium carbonate.

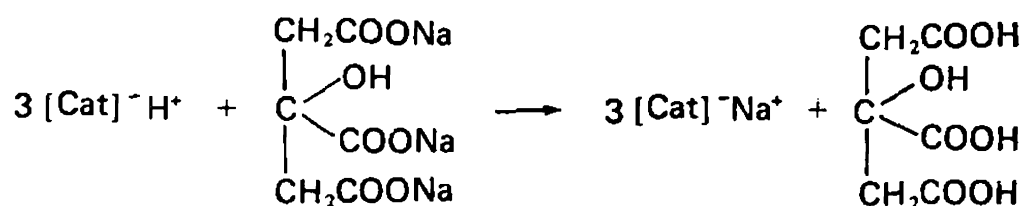
The drug is analysed for the sodium ion (it colours a flame yellow) and for the citric acid residue. The most characteristic reaction for the citrate ion is that with calcium chloride or hydroxide. When a calcium chloride solution is added to sodium citrate in the cold, a transparent solution forms, but when heated it becomes turbid owing to the formation of calcium citrate, insoluble in hot water; when cooled, the precipitate dissolves again:



The drug must contain no admixtures of arsenic, tartaric acid, oxalates, and other organic impurities.

The content of sodium citrate in the drug can be determined in several ways:

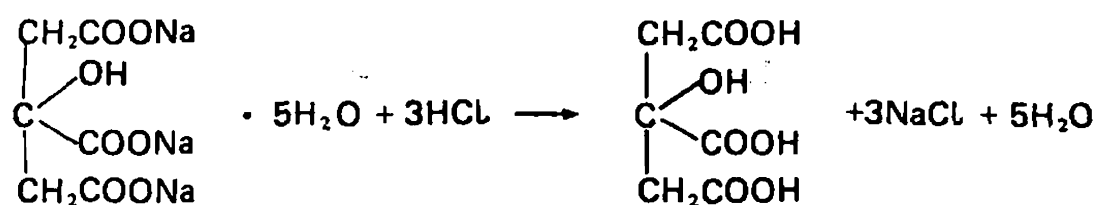
(a) by ion-exchange chromatography, using the cation exchanger KY-2 in the H form:



The evolved citric acid is titrated with an alkali using phenolphthalein as the indicator (the pharmacopoeial method);

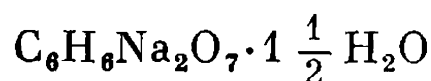
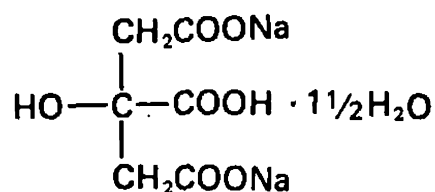
(b) by neutralization; the direct titration of sodium citrate with an acid using a methyl orange indicator in the presence of ether,

which extracts the citric acid evolving during titration (this method has been proposed by Z. Umansky):



The drug creates an alkali reserve in the blood. Its 10% aqueous solutions have a pH of 7-7.5. But the main use of the drug is to prevent the coagulation of blood, and it is therefore used as a blood preservative when storing large amounts of blood for medical purposes. This drug played an especially important role during World War II.

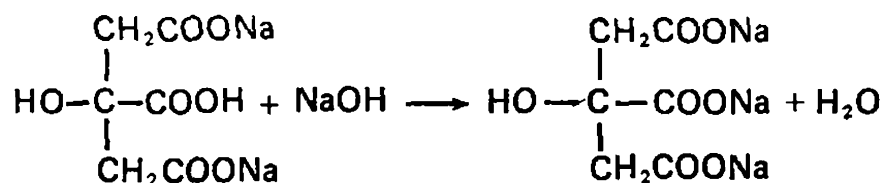
Sodium Acid Citrate for Injections (*Natrii hydrocitrates pro injectionibus*)



M.m. 263.11

Sodium acid citrate (disubstituted) forms colourless crystals or a white crystalline powder with an acidic taste. It is similar in its properties to the trisodium salt, and therefore all the reactions of the latter also relate to this drug.

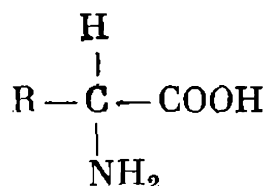
The content of the substance in the drug is determined by neutralization (the pharmacopoeial method):



It should be stored in well closed jars.

Chapter 15. Amino Acids of the Aliphatic Series

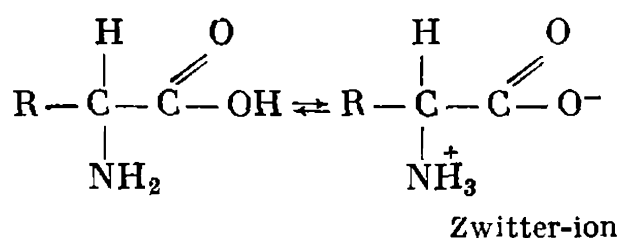
Carboxylic acids containing an amino group in addition to the carboxyl one are called amino acids:



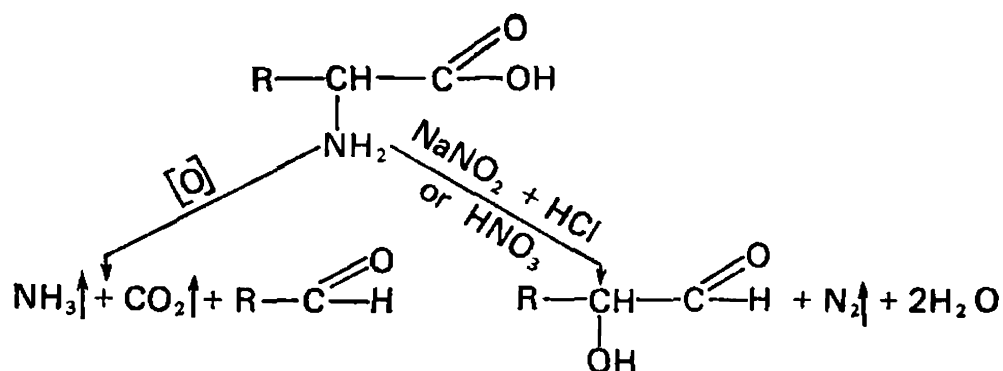
The amino acids are abundant in nature and are structural elements of protein molecules. They play an important role in biological processes.

The amino acids of the aliphatic series have an amphoteric nature because of the presence of an acidic ($-\text{COOH}$) and basic ($-\text{NH}_2$) group. Hence, they form salts with alkalies and mineral acids.

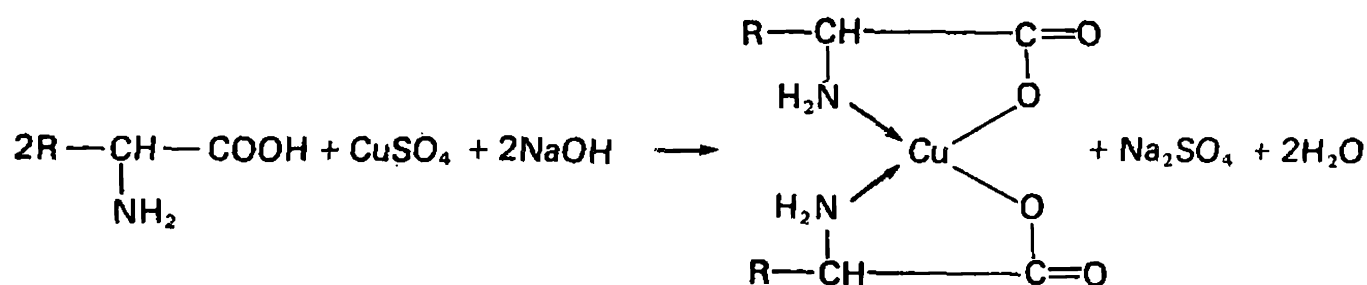
Being amphoteric electrolytes, amino acids exist in the form of bipolar or zwitter-ions (inner salts) both in aqueous solutions and in the solid state:



One of the features of amino acids is their ability to be readily oxidized to ammonia, carbon dioxide, and an aldehyde, while if oxidizing agents such as sodium nitrite in an acidic medium or nitric acid are used, the oxidation proceeds to molecular nitrogen with the simultaneous formation of hydroxyacids:



Amino acids are characterized by the formation of copper salts in which the copper ion is bound by additional valences to the nitrogen atoms, forming a complex ion of a dark blue colour:

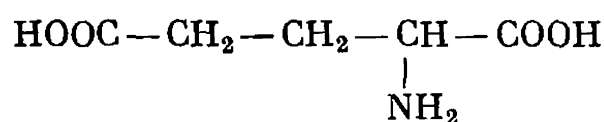


This colour reaction is used to identify amino acids. All the acids of the aliphatic series react with ninhydrin. The product of this reaction is coloured, which is used for identification.

Of the amino acids of the aliphatic series, glutaminic acid, methionine, and aminaloni are employed the most in medicine. The first two preparations are pharmacopoeial ones.

Glutaminic Acid (*Acidum glutaminicum*)

1-Aminoglutaric Acid



$\text{C}_5\text{H}_9\text{NO}_4$

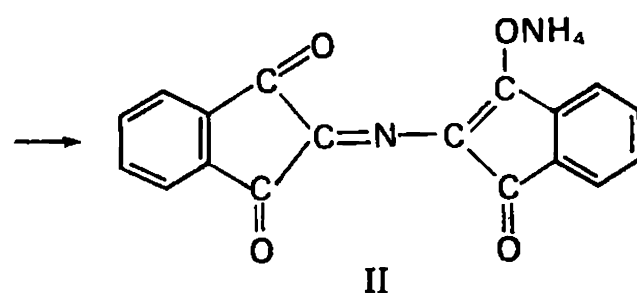
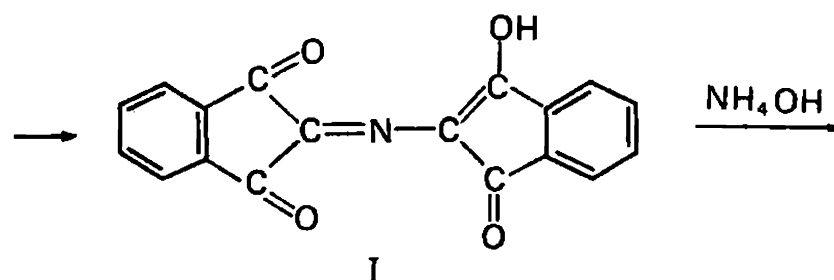
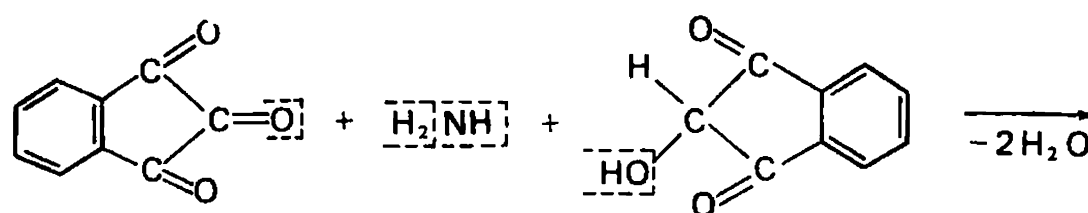
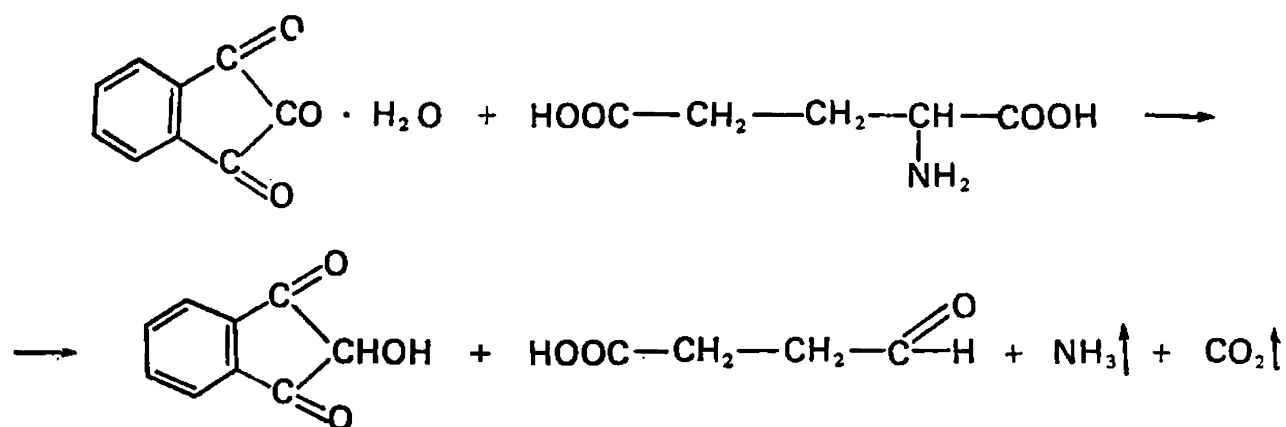
M.m. 147.13

The chemical name of glutaminic acid (glutamic acid) is 1-aminoglutaric acid. It is contained in a number of proteins such as myosin, casein, and 2-lactoglobulin. A large amount of glutaminic acid is contained in the proteins of the brain and in cereals. It was formerly produced exactly from cereals by acid hydrolysis. At present, glutaminic acid is synthesized.

Glutaminic acid is a white crystalline powder with an acidic taste. It dissolves sparingly in cold water and better in hot water. It does not dissolve in organic solvents. Being an amphoteric compound, it dissolves in acids and alkalies to form salts.

Glutaminic acid is identified by its reaction with ninhydrin. The essence of this reaction consists in that the ninhydrin oxidizes the glutaminic acid and decomposes it into an aldehyde, carbon dioxide, and ammonia. The evolving ammonia condenses with the second molecule of the ninhydrin and with the product of its reduction—di-

ketohydroxyhydrinden:



Blue-violet

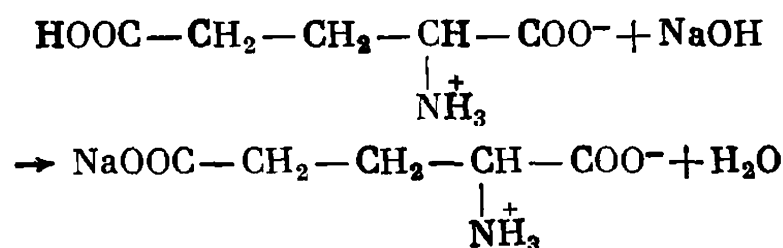
The ammonium salt (II) of the enol form of the obtained compound (I) has an intensive blue-violet colour.

When glutaminic acid, like other amino acids, reacts with copper sulphate in an alkaline medium, a coloured copper complex forms which is also used for analysis.

The State Pharmacopoeia recommends the quantitative determination of glutaminic acid in the drug using two methods:

(a) by the amount of fixed nitrogen, which is determined by the Kjeldahl method;

(b) by neutralization; the glutaminic acid is titrated with a sodium hydroxide solution in the presence of bromothymol blue until the yellow colour changes to a light bluish-green one:



Glutaminic acid participates in the process of nitrogen metabolism in an organism. It binds the ammonia formed during metabolism and thus facilitates its detoxification.

Glutaminic acid is employed in medicine in diseases of the central nervous system, chiefly in various psychic disorders. It is taken orally in the form of 0.25-g powders or tablets, more rarely intravenously in the form of a 1% solution. It is dispensed in the form of powders, ampoules, coated tablets, or tablets dissolving in the intestine, each containing 0.25 g of the drug.

It should be kept in a well closed container in a place protected from light.

In addition to glutaminic acid, its calcium and magnesium salts are used in medicine. The indications for their use are the same as for the parent acid.

Aminalon (*Aminalonum*)



$\text{C}_4\text{H}_9\text{NO}_2$

M.m. 103.12

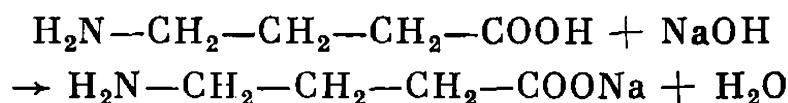
In its chemical structure, aminalon (GABA) is 3-aminobutyric acid. It is a synthetic Soviet drug with a psychotropic action identical to the Japanese drug Gammalon.

3-Aminobutyric acid is a biogenic substance. It is contained in the central nervous system and participates in metabolic processes in the brain, therefore aminalon is chiefly used in vascular diseases of the brain.

Aminalon is a white crystalline powder with a slightly bitter taste and a weak specific odour of amino acids. It dissolves readily in water and very sparingly in alcohol; the pH of a 5% aqueous solution is 6.5-7.5.

Aminalon can be tested by all the reactions characteristic of amino acids of the aliphatic series such as a reaction with ninhydrin, and with copper salts.

The content of aminalón in the drug, like that of glutaminic acid, is determined by neutralization:



The drug is dispensed in the form of coated 0.25-g tablets. It should be stored in a dry place protected from light.

REVIEW QUESTIONS

1. Which functional group characterizes a molecule of a carboxylic acid of the aliphatic series?
2. How does the carboxyl group affect the solubility of substances in water?
3. How does the carboxyl group affect the physiological activity of substances?
4. Why have the carboxylic acids of the aliphatic series not found widespread application in medicine?
5. What underlies the chemical properties of the carboxylic acids?
6. Substantiate the possibility of determining sodium citrate by ion-exchange chromatography.
7. Why can the quantitative determination of sodium citrate be performed by neutralization? For what purpose is ether added in the given case?
8. What explains the statement that sodium citrate was of a great value during the years of World War II?
9. In what does sodium citrate differ from sodium acid citrate?
10. In the quantitative determination of glutaminic acid by titration with an alkali, why does the substitution of hydrogen by sodium occur only in the carboxyl group remote from the amino group?
11. What properties underlie the quantitative determination of aminalón by non-aqueous titration?

PRACTICAL LESSON

Analysis of Sodium Citrate

Perform the quantitative determination of the sodium citrate in the drug by ion-exchange chromatography according to the State Pharmacopoeia.

1. Write the equations of the chemical reactions.
2. Make the required calculations and conclusions.
3. Assess the method of ion-exchange chromatography.

Analysis of Sodium Acid Citrate

1. Perform an identification reaction.

Dissolve a small amount of the analyte drug in water and add a calcium chloride solution. When the solution is heated (boiled), a white precipitate forms that dissolves in hydrochloric acid. Write the equations of the chemical reactions.

2. Conduct a quantitative determination (neutralization—express analysis).

Dissolve a sample of the drug weighing 0.1 g in 10 ml of water, add three drops of phenolphthalein and titrate with a 0.1 *N* solution of sodium hydroxide until a pink colour appears. Write the equation of the chemical reaction.

3. Calculate the content of the sodium acid citrate in the preparation in per cent by formula (1.1):

$$X = \frac{VKT}{a} \times 100 = \frac{VK \times 0.0236}{0.1} \times 100$$

where V is the volume of a 0.1 N sodium hydroxide solution, ml, $T = 0.0236$ g/ml, and a is the mass of the drug taken for the determination, g.

According to the requirements of the State Pharmacopoeia, the content of $C_6H_8Na_2O_7 \cdot 1\frac{1}{2}H_2O$ should be at least 98.5% and at most 101.5%.

4. Compare the obtained result with the requirements of the State Pharmacopoeia and make the corresponding conclusion.

Analysis of Glutaminic Acid

Control the quality of glutaminic acid with respect to all indices according to the requirements of the pharmacopoeia in force in your country.

Chapter 16. Ethers and Esters

Only a few compounds having an ether or ester group alone as their functional group are employed in medicine. The best known preparations of this series are diethyl ether, dimedrol, nitroglycerin, and amyl nitrite. But there are numerous drugs whose molecules in addition to other functional groups contain either an ether or an ester group. Examples are local anaesthetics [novocaine (procaine), anesthesin (benzocaine), dicaine (tetracaine)], tropanic and indolic alkaloids, many hormones, and vitamins.

Esters are encountered widely in nature. The pleasant aromas of flowers, fruit, and berries are due substantially to the presence of esters in them.

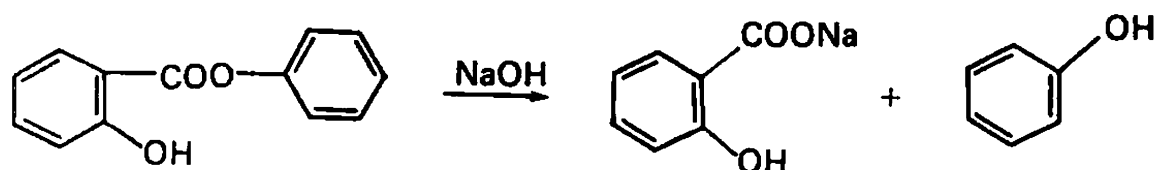
Ethers and esters find the most diverse applications in medicine. The lower ethers are volatile and unlike esters are inert substances of a neutral nature. These properties are what determines their use for inhalation narcosis (ether for narcosis).

The higher ethers are solid crystalline substances having a different application.

Drugs are sometimes purposefully converted into esters to prolong their action. For example, corticosteroids in the form of acetates and androgen hormones in the form of propionates have a more prolonged action.

Sometimes an ester is used as the initial form of a drug to provide a directed action in an organism. For example, the phenyl ester of salicylic acid (phenyl salicylate) decomposes in the intestine under

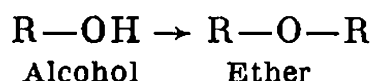
the influence of the alkaline medium with the evolution of phenol, therefore it is just in the intestine that it has an antiseptic action:



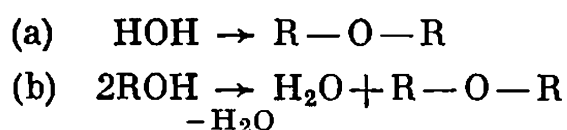
Both ethers and esters readily dissolve in organic solvents, while diethyl ether is itself a good organic solvent and is often used for the extraction of active principles, for example from plant raw material, or for the separation of certain bases from complex drug mixtures.

16.1. ETHERS

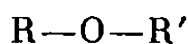
Ethers can be considered as the products of substitution of the hydrogen atom in the hydroxyl of an alcohol by a radical (R):



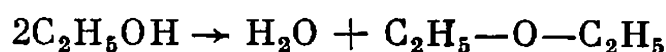
Ethers can also be considered as derivatives of water (a) in whose molecule the hydrogen atoms have been replaced by radicals, and as anhydrides of alcohols (b):



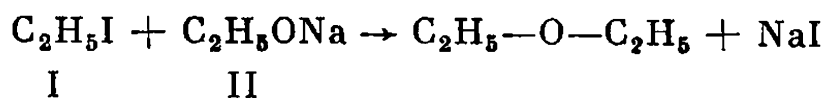
If the radicals in an ether molecule are different, the ethers are said to be **mixed**:



Ethers are chiefly produced by the dehydration of alcohols in the presence of water-removing agents (sulphuric or phosphoric acid, anhydrous salts such as CuSO_4 and ZnCl_2):



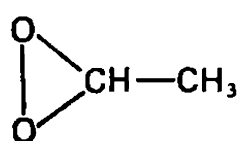
They can also be produced from alkyl halides (I) and sodium alcohates (II) by an exchange reaction:



This method is used more frequently under laboratory conditions to produce mixed ethers (with different radicals).

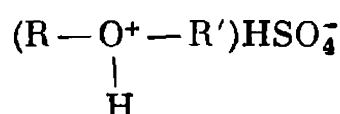
An ether produced in any way is purified from admixtures, is dried by letting it stand with dehydrated salts, and is distilled at a definite temperature. It must be had in view, however, that ethers

unlike esters can be readily oxidized even by the oxygen of the air to peroxides that are a major hazard in the distillation of the ethers and can be the cause of explosions. The product of oxidation of medical ether is ethylidene peroxide, which is exactly what causes an explosion:



Consequently, prior to distilling an ether or determining its boiling point, it should be tested for the presence of peroxides.

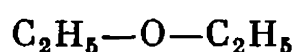
A feature of ethers is their ability to form oxonium salts with concentrated acids. This is due to the fact that the oxygen of an ether has two pairs of free electrons that attract a proton of an acid:



Oxonium salts are similar to ammonium ones, but unlike the latter are less stable and easily decompose in the presence of water. The formation of oxonium salts is used in pharmaceutical analysis, for example for the identification of dimedrol (diphenhydramine), because some of these salts are coloured (see the reactions of identification of dimedrol on p. 193).

Of the ethers, medical ether (diethyl ether) and dimedrol are pharmacopoeial preparations.

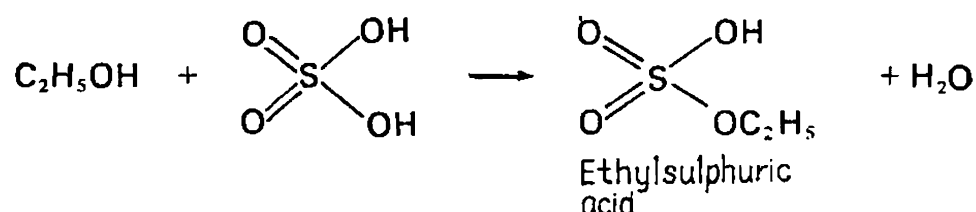
Medical ether (*Aether medicinalis*)



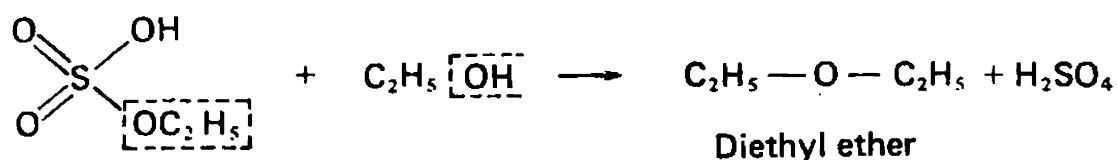
$\text{C}_4\text{H}_{10}\text{O}$

M.m. 74.12

Medical ether (diethyl ether, ethyl ether) can be produced in one of the ways described above, but the hydration of alcohol in the presence of sulphuric acid is the common industrial process:



The ethylsulphuric acid reacts with the remaining alcohol to form ether:



After purification from possible admixtures and drying, the ether is distilled and the distillate is collected at a temperature of 34-35 °C.

The State Pharmacopoeia lists two ether preparations, namely, medical ether and ether for narcosis (*Aether pro narcosi*). Both drugs are produced in the same way, have the same chemical properties, and differ only in the degree of their purity.

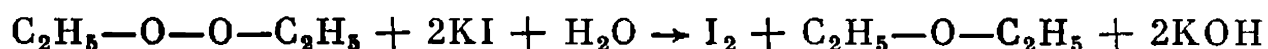
Ether is a colourless, transparent, very mobile liquid with a burning taste and a peculiar odour. It dissolves in water, mixes in all proportions with alcohol, chloroform, and readily ignites. A mixture of ether vapour with oxygen or nitrous oxide easily explodes.

The preparation is identified by its physical indices, namely, its boiling point (34-35 °C) and its specific gravity (0.715-0.718).

During its production, ether can be contaminated with various admixtures such as acetaldehyde, which is detected by using Nessler's reagent. Other possible admixtures are acetic acid and the product of sulphuric acid reduction—sulphur dioxide. The State Pharmacopoeia establishes a definite limit of the acidity.

Ether can also be contaminated with an admixture of fusel oils (from alcohol) that are detected when the ether is evaporated from filter paper; the latter after the evaporation of the ether must have no odour of fusel oils.

Peroxide compounds are a dangerous admixture. They form as a result of the contact of the ether with the air when standing and are a product of its oxidation. Peroxide compounds can be detected in ether by a reaction with a potassium iodide solution. If peroxide compounds are present, they oxidize the ionogenic iodine in the potassium iodide to molecular iodine that colours the ether yellow:



To remove the peroxide compounds, the ether is shaken with an iron(II) sulphate solution, is next dried, and distilled. Iron(II) is readily oxidized by the peroxide to Fe(III), while the peroxide compounds decompose.

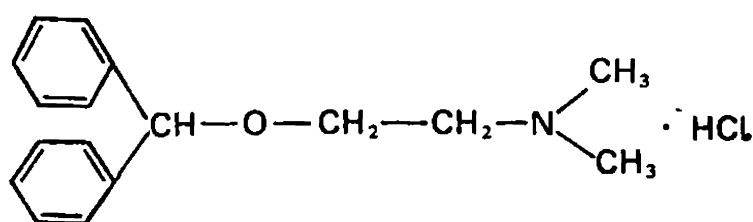
Ether for narcosis must have a higher purity. For example, before pouring the ether into orange glass bottles for dispensing, an additional test for aldehydes must be made with Nessler's reagent which should produce a negative reaction for aldehydes during 25 minutes. An admixture of water is controlled in ether for narcosis with the aid of picric acid. The colour produced by this acid must not be more intensive than that of a reference.

The inhalation of large amounts of ether causes a state of intoxication and complete narcosis. This explains its use in surgery for narcosis inhalation. Ether is also used for local anaesthesia. It is administered orally very rarely to stop vomiting.

Ether is stored with care (group B) in well closed orange glass bottles in a cool place protected from light and far from a fire.

Ether for narcosis is dispensed and stored in hermetically sealed bottles filled up to their top (to exclude the action of atmospheric oxygen). The stopper must be wrapped in metal foil to prevent the substances contained in it from getting into the ether. The label must bear the inscription "*Aether pro narcosi*", and also the series and date of production. The bottles are opened for use immediately before an operation. If a bottle is open even a few hours before an operation, such ether is no longer suitable for narcosis. The preparation must be checked every six months.

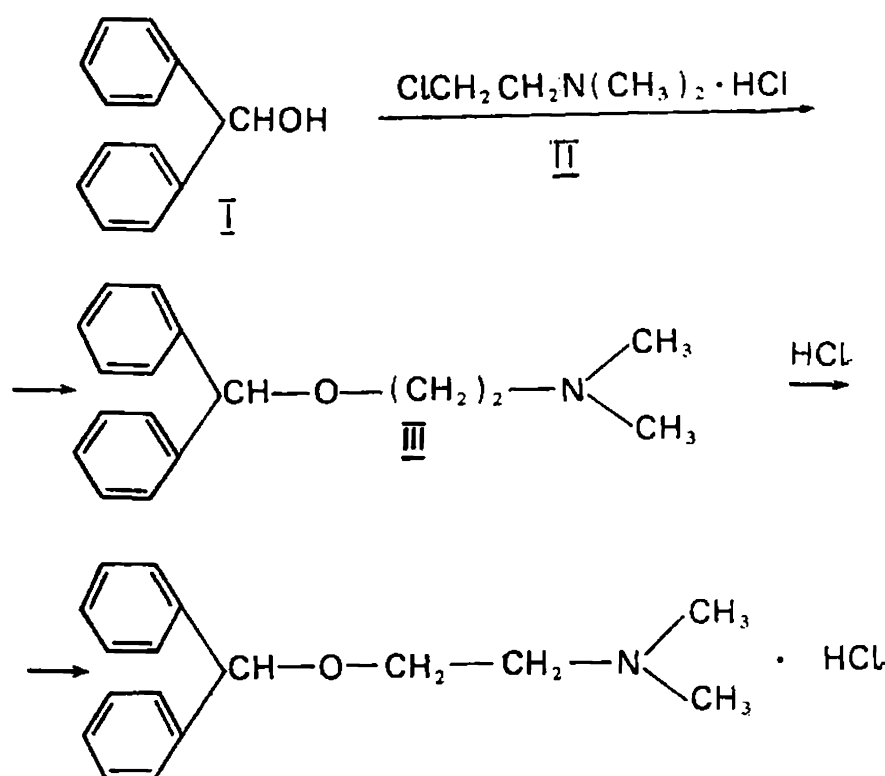
Dimedrol (*Dimedrolum*)



$\text{C}_{17}\text{H}_{21}\text{NO} \cdot \text{HCl}$

M.m. 291.82

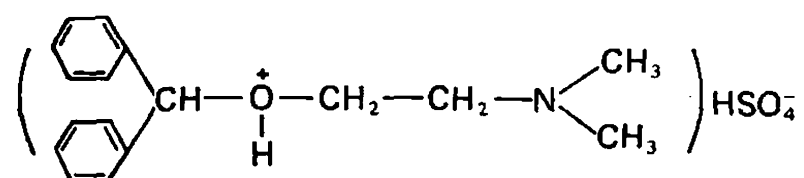
Dimedrol (diphenhydramine, benzhydramine) is produced by reacting benzhydrol (I) and the hydrochloride of *para*-dimethylaminoethylchloride (II) in the presence of an alkali. The resulting base (III) is transformed by the action of hydrochloric acid into the hydrochloride—dimedrol:



Dimedrol

Dimedrol is a white finely crystalline powder without an odour or with a hardly perceptible one and with a bitter taste. When tasted, it causes a feeling of numbness on the tongue. It is hygroscopic. Dimedrol dissolves very readily in water, readily in alcohol and chloroform, and very poorly in ether and benzene.

Of the identification reactions, the most characteristic for dimedrol is the reaction of formation of coloured oxonium salts with concentrated acids. For example, when dimedrol is reacted with concentrated sulphuric acid, an oxonium salt forms whose colour ranges from yellow to brick red:

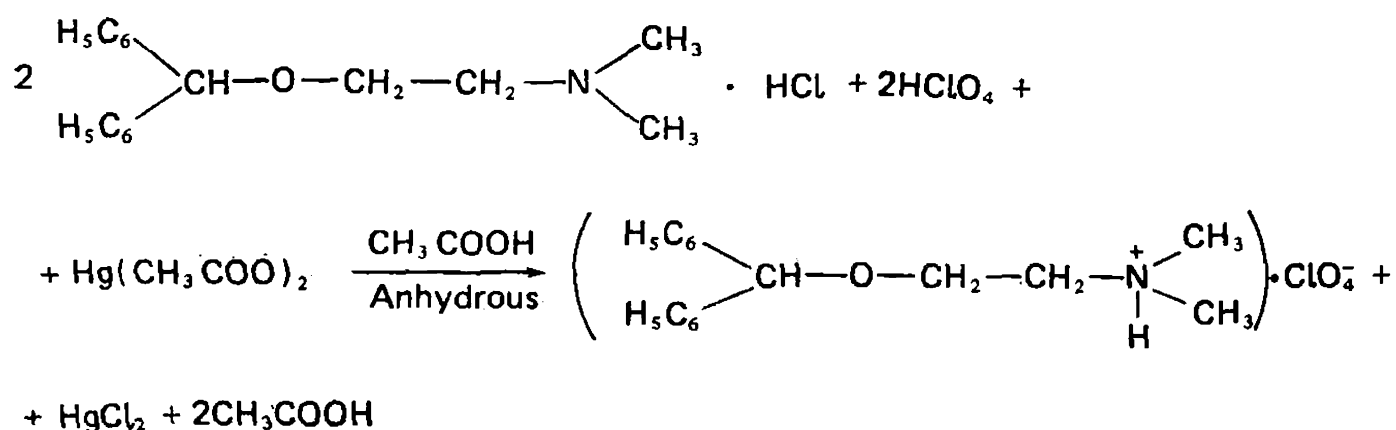


When water is added, the colour vanishes, which is associated with the decomposition of this salt.

Dimedrol can also be identified by the evolution of benzhydrol, which forms when the drug is heated with dilute hydrochloric acid. The crystals of benzhydrol precipitate after cooling of the reaction mixture. When recrystallized and dried, they have a melting point of 62-67 °C.

The chloride ion is determined with a silver nitrate solution. All these reactions are pharmacopoeial ones. The drug may contain admixtures of sulphates and heavy metals within the standard limits stipulated by the State Pharmacopoeia.

The content of the drug is determined by acid-base titration in non-aqueous media (the pharmacopoeial method):



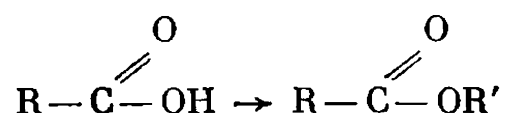
Dimedrol can also be determined quantitatively relative to the bound hydrochloric acid by argentometry.

Dimedrol is used as an active antihistaminic (antiallergic) drug. It is administered in allergy, and also as a light soporific.

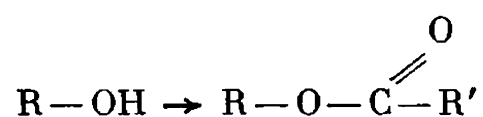
It is dispensed in 0.03- and 0.05-g powders and tablets and in ampoules containing 1 ml of a 1% solution. It should be stored in well closed containers protected from light and moisture. It is listed in Group B.

16.2. ESTERS

Esters can be considered as derivatives of acids in which the hydrogen of the carboxyl group has been substituted by a radical (R'):



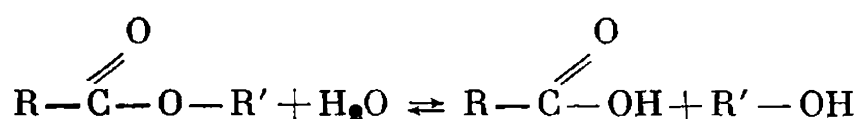
They can also be considered as derivatives of alcohols in whose molecule the hydroxyl hydrogen has been substituted by an acid residue:



The preparation of esters consists in reacting the relevant alcohol and acid in the presence of water-removing agents or in reacting an alcohol with acid anhydrides (amyl nitrite).

The low-molecular esters are mobile liquids with a characteristic specific odour, while the high-molecular esters are solids. All the esters are insoluble in water and well soluble in organic solvents. If an ester has been formed by an acid that is an oxidizing agent, it is explosive because intramolecular oxidation of the alcohol is possible. An example is nitroglycerin.

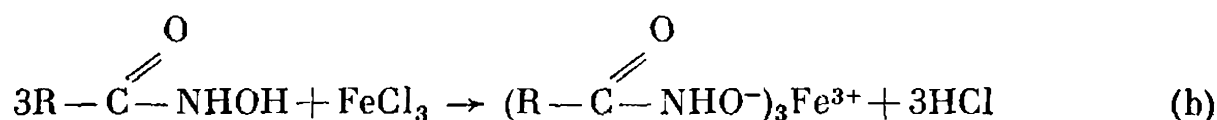
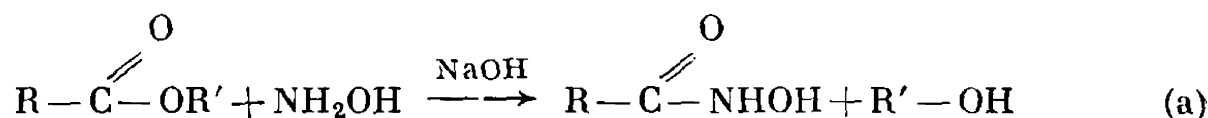
A feature of esters is their ability to readily hydrolyze. The hydrolysis is catalyzed by alkalies, acids, heating, and by oxidizing and reducing agents:



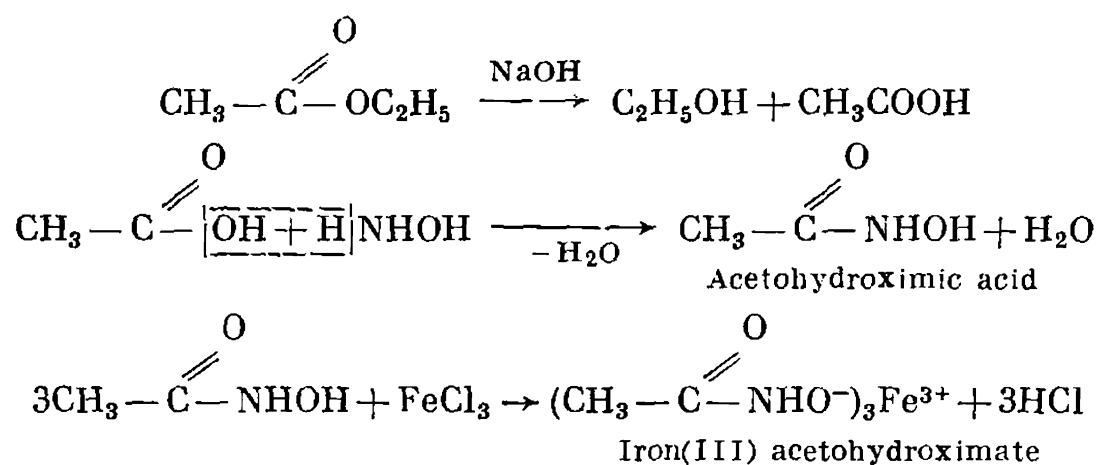
The hydrolysis products are exactly what is used to identify esters, and since the hydrolysis products of each ester are different, this characterizes their individuality.

A common reaction for esters is the formation of salts of the hydroximic acids (hydroximates), which are mostly coloured. The latter circumstance is used for identification of an ester group in a molecule of any preparation. The essence of this reaction consists in that in the alkaline hydrolysis (at pH > 13) of esters in the presence of hydroxylamine, hydroximic acids (a) form. The products of their

reaction with salts of heavy metals (most often salts of Fe^{3+} and Cu^{2+} are employed) are hydroximates (b):



We can give this reaction with ethyl acetate as a specific example:

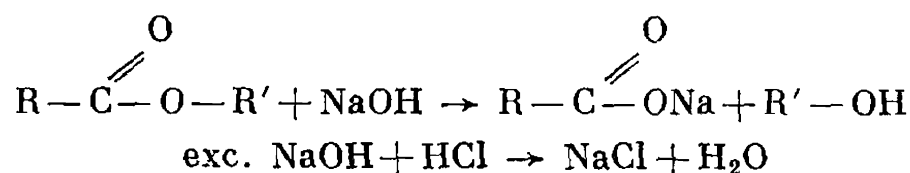


The colour of hydroximates varies depending on the composition of the formed salt.

However, the reaction of hydroximate formation cannot be considered as specific for esters because it also occurs with amides and acid anhydrides, as well as lactones. Hence, it is a group reaction for carboxylic acid derivatives (ethers, esters, lactones, amides, carboxylic acid anhydrides).

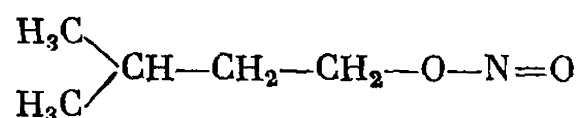
Possible admixtures in esters are the products of their hydrolysis (alcohol, acid).

The general principle underlying the quantitative determination of esters consists in their alkaline hydrolysis using a standard alkali solution whose excess is titrated with an acid:



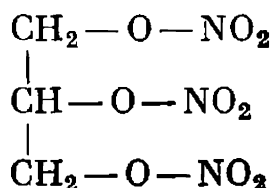
The pharmacopoeial preparations of the ester group include amyl nitrite* and nitroglycerin.

* Amyl nitrite is an ester of isoamyl alcohol and nitrous acid:



It is used as a spasmolytic (vasodilating) drug.

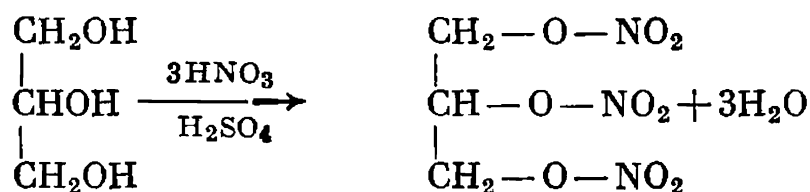
Nitroglycerin (*Nitroglycerinum*)



M.m. 227.09

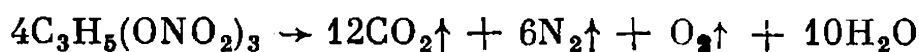
Nitroglycerin (glyceryl trinitrate, trinitroglycerin) is an ester of nitric acid and the triatomic alcohol glycerin. It is produced by adding a mixture of nitric and sulphuric acids to a calculated amount of glycerin. The formed nitroglycerin gathers as an oil over the acid layer. It is separated, washed several times with water, a diluted soda solution (to neutralize the acid), and then again with water. After this, it is dried with anhydrous sodium sulphate.

The reaction of nitroglycerin formation can be represented schematically as follows:



Nitroglycerin is a heavy oily liquid (its specific gravity at 5 °C is 1.601) with a sweet taste. It is insoluble in water, but dissolves well in organic solvents. It is very poisonous.

A feature of nitroglycerin is its ability when jolted or heated to explode owing to its decomposition with the evolution of an enormous volume of strongly heated gases:



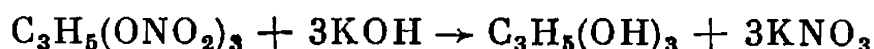
Consequently, if one has spilled out an alcohol solution of nitroglycerin and there is a danger of an explosion after the alcohol evaporates, one must treat the spilled out nitroglycerin with a solution of an alkali or sodium carbonate to hydrolyze the nitroglycerin. The products of its hydrolysis are not dangerous.

Nitroglycerin is employed in medicine in the form of two drugs:

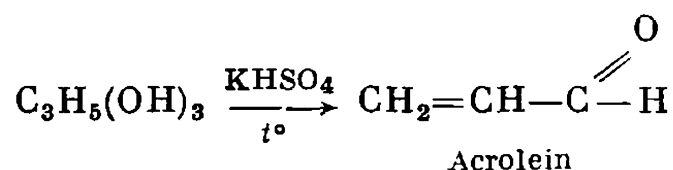
1. Tablets of nitroglycerin (*Tabulettae Nitroglycerini*).
2. An alcohol solution of nitroglycerin 1% (*Solutio Nitroglycerini* 1%).

The latter drug is a colourless transparent solution with a neutral reaction (its specific gravity is not over 0.829).

The hydrolysis of nitroglycerin in the presence of an alkali yields glycerin and a nitrate:

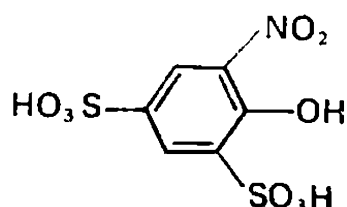


If potassium hydrogen sulphate is added to the products and the mixture is heated to 180 °C, a pungent characteristic smell of acrolein appears (the reaction for glycerin):



The nitric acid residue is determined by the action of a sulphuric acid solution of diphenylamine; the mixture will acquire a deep blue colour.

For the quantitative determination of a 1% alcohol solution of nitroglycerin, the State Pharmacopoeia recommends the photocolorimetric method. In this case, the nitroglycerin is first subjected to acidic hydrolysis. Phenoldisulphonic acid is added to the hydrolysis products and reacts with the nitric acid formed as a result of the hydrolysis of the nitroglycerin. A yellow nitroderivative of phenoldisulphonic acid forms. Its colour is intensified by the addition of an ammonia solution:



The optical density of the coloured solution is determined at 410 nm, because at this wavelength the given compound has the maximum optical density. The nitroglycerin content in the drug is determined for the obtained value of the optical density by means of a calibration graph plotted for potassium nitrate.

Nitroglycerin is used in medicine as a spasmolytic (vasodilating) agent in angina pectoris. Its action is similar to that of amyl nitrite, but in comparison with the latter is slower and more prolonged. When a nitroglycerin solution is taken orally, a piece of sugar is wetted with the drug and held in the mouth up to complete dissipation.

The drug is dispensed in bottles containing 5-10 ml of a 1% alcohol solution and in tablets each containing 0.5 mg of pure nitroglycerin. Keep the bottles with a nitroglycerin solution in a cool place protected from light and far from a fire. It is listed in Group B.

Sustac dispensed in tablets is a special medicinal form of nitroglycerin with sustained release. When taken orally, a part of the tablet is assimilated rapidly and produces an effect already in 10 minutes. The other part of the tablet is assimilated slowly and its action continues for several hours. This makes it possible to prevent attacks of angina pectoris in chronic coronary insufficiency. This drug is produced in the Socialist Federal Republic of Yugoslavia.

REVIEW QUESTIONS

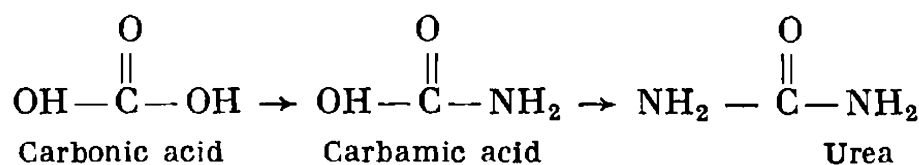
- Ethers. 1. Characterize the reactivity of ethers.
2. What process occurs when ethyl ether is left in the light and in the air? Write the equation of the chemical reaction.
3. Why does the purity of medical ether have to be checked every six months?
4. Why does medical ether have to be stored far from a fire?
5. Why do bottles have to be filled with medical ether to the top when preparing it for dispensing?
6. Why is it necessary to wrap the stoppers closing bottles with medical ether in metal foil?
7. Why does the colour of the oxonium salt of dimedrol vanish when water is added?
8. Why can the quantitative determination of dimedrol be performed by acid-base titration in non-aqueous media?
9. Why must dimedrol be protected from moisture and light?
- Esters. 1. Which compounds are called esters?
2. What are lactones?
3. Which esters are explosive? Explain this from a chemical viewpoint.
4. What chemical properties do esters have?
5. What underlies the quantitative determination of esters?
6. What requirements must the storage of a solution of nitroglycerin meet?
7. You have broken a bottle containing a solution of nitroglycerin (or spilled it out). How can an explosion be prevented? Write the equation of the chemical reaction.

Chapter 17. Amides of Carbonic Acid and Their Derivatives

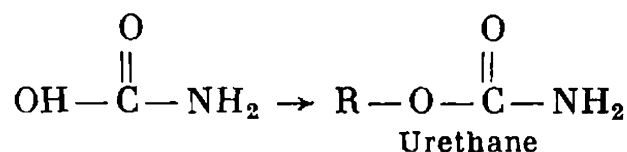
Carbonic acid, like many other acids, forms a number of derivatives such as salts, esters, acid chlorides, and amides.

Of major interest for medicine are the amides of carbonic acid because their derivatives are valuable drugs.

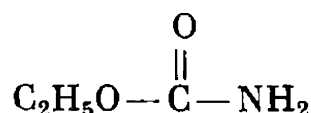
Carbonic acid, being a dibasic one, forms two types of amides, namely, (a) a half or partial amide (the product of substitution of one hydroxyl by an amino group), i.e. carbamic acid, and (b) the complete amide (the product of substitution of two hydroxyls by amino groups), i.e. carbamide, or urea:



Carbamic acid is highly unstable in the free state and decomposes into carbon dioxide and ammonia. But its acid chlorides, salts, and esters are well known. Of importance in medicine are the esters of carbamic acid known as urethanes, which have a soporific action:

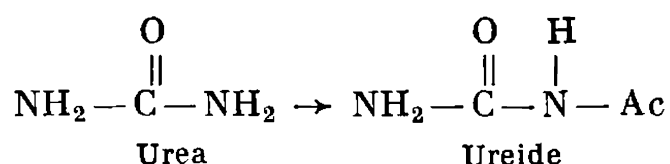


Ethyl carbamate is the simplest urethane. Its formula is:



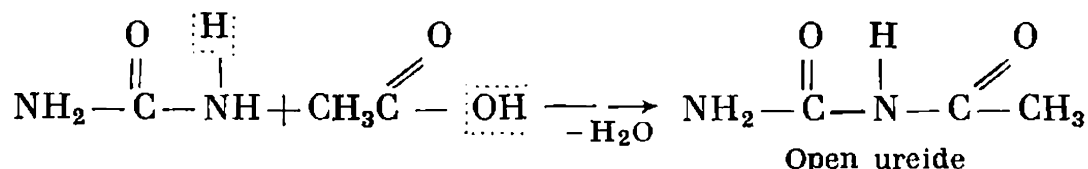
A variety of urethanes can be prepared depending on the alcohol used for the esterification of carbamic acid.

Among the derivatives of urea, the greatest interest for medicine are its acyl derivatives in which the hydrogen of the amino group of urea is substituted by an acid residue—acyl (Ac stands for the residue of any acid):

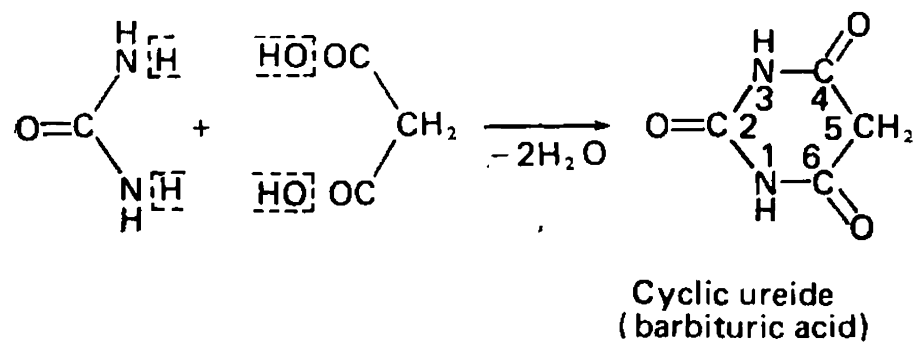
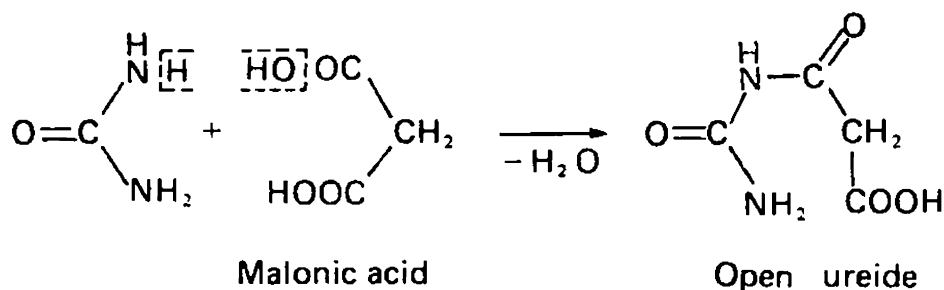


Acyl derivatives of urea were first prepared by N. Zinin, who named them **ureides**.

When urea is reacted with a monobasic carboxylic acid, open (acyclic) ureides form:



When urea is reacted with a dibasic carboxylic acid, both open and closed (cyclic) ureides can form depending on the reaction conditions:



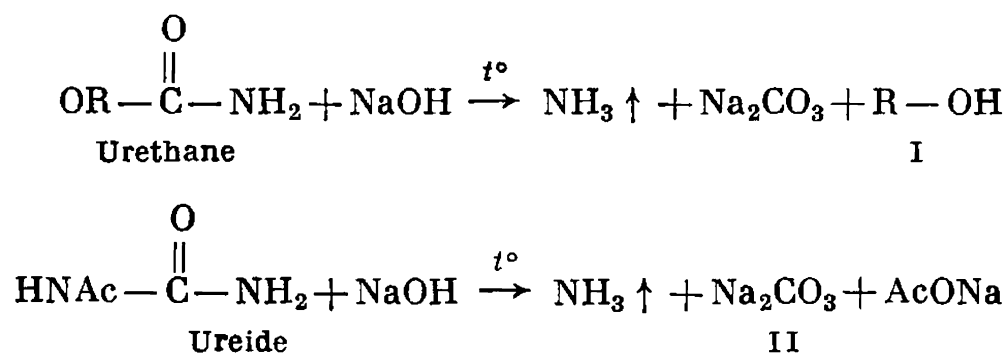
When the hydrogens in the methylene group (position 5) of a barbituric acid are substituted by various radicals, a multitude of its

derivatives (barbiturates) used in medicine as soporific drugs can be produced.

As regards their physical properties, drugs relating to ureides and urethanes are solid white crystalline substances sparingly soluble in water, except for salts.

The ureides and urethanes have a number of common chemical properties. When heated with an alkali, they evolve ammonia and sodium carbonate, and when an acid is added, the sodium carbonate evolves gas bubbles (CO_2).

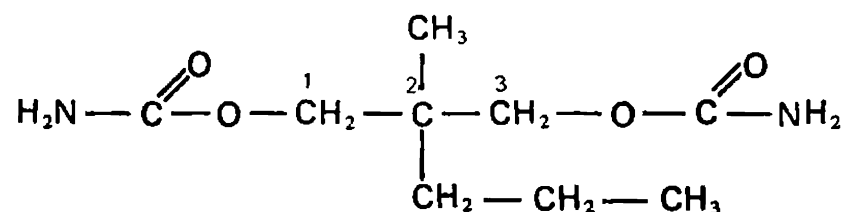
The other products formed when urethanes and ureides react with an alkali make it possible to distinguish them from one another. When dealing with urethanes, an alcohol forms (I), and with ureides, the sodium salt of the relevant acid (II):



A representative of the urethanes is the drug meprotan, and of the open ureides is the drug bromisoval.

Meprotan (*Meprotanum*)

2-Methyl-2-propyl-1,3-propanediol dicarbamate



$\text{C}_9\text{H}_{18}\text{N}_2\text{O}_4$

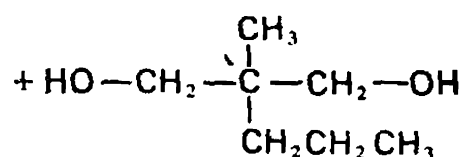
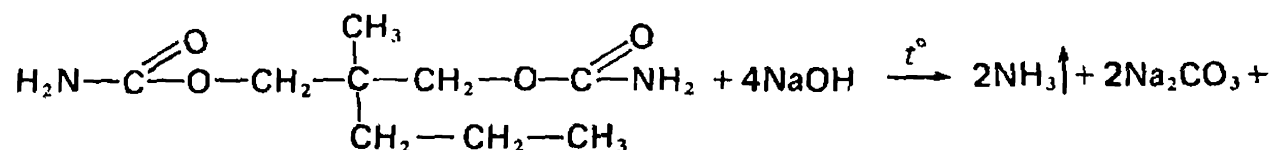
M.m. 218.25

The drug was synthesized at the USSR Ordzhonikidze Chemico-Pharmaceutical Research Institute.

Meprotan (meprobamate, procalmadiol) is a white crystalline powder with a characteristic odour and taste. It dissolves sparingly in water and ether, and readily in 95% alcohol and acetone.

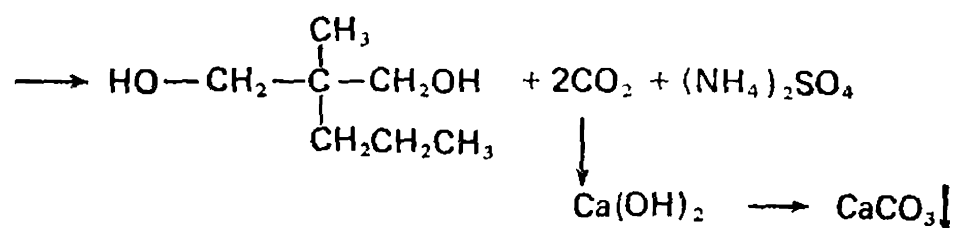
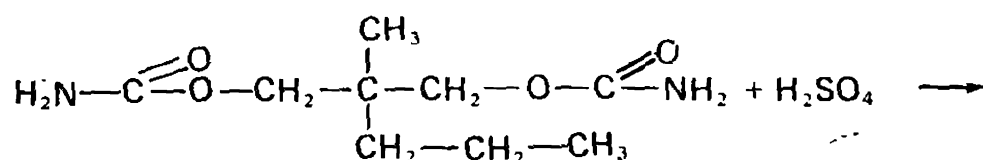
Being an urethane, meprotan is decomposed by an alkali with the formation of ammonia, which is determined by its smell or by

wet red litmus paper turning blue:

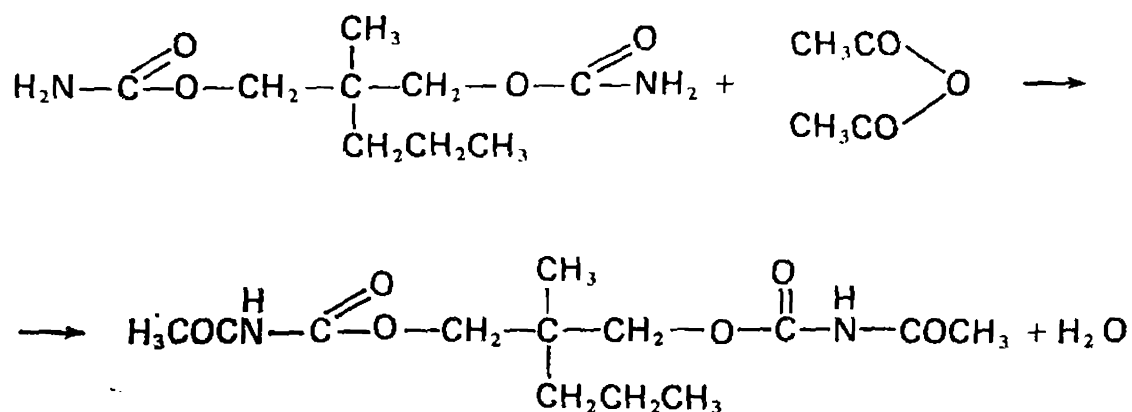


2-Methyl-2-propyl-1,3-propandiol

When the drug is heated with concentrated sulphuric acid, carbon dioxide evolves. The latter is identified by passing it through lime water which becomes turbid:



The amino groups in a meprotran molecule can be acetylated. This is done with acetic acid anhydride. The diacetyl derivative of meprotran should have a melting point of 123-125 °C:



Diacetyl derivative of meprotran

All these reactions are official ones for identifying the drug. The latter may contain admixtures of chlorides, sulphates, heavy metals, and arsenic. The State Pharmacopoeia tolerates the content of

these admixtures in the drug within standard limits. The limit of acidity and alkalinity in the drug is also established.

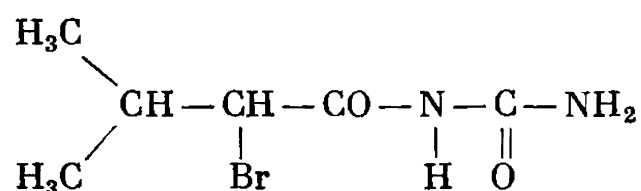
The quantitative determination of the drug is performed by finding its nitrogen content using Kjeldahl's method.

Meprotran has a tranquilizing action on the central nervous system and amplifies the action of soporifics. It is administered in the treatment of nervous and psychic diseases.

It is dispensed in powders and tablets. It should be stored in well closed containers. It belongs to Group B drugs.

Bromisoval (*Bromisovalum*)

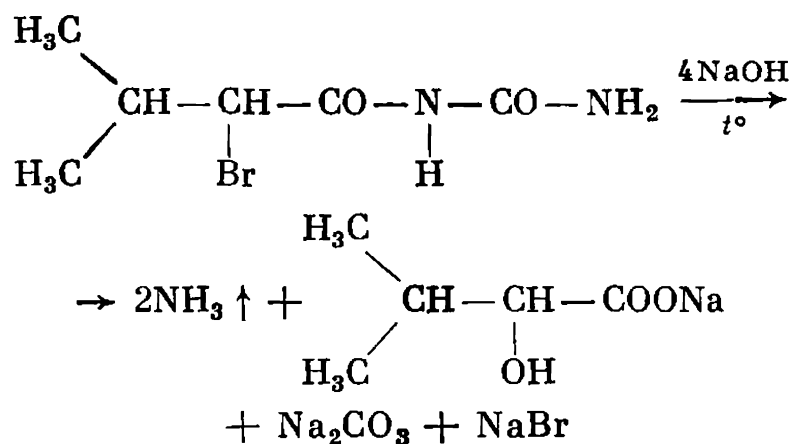
1-Bromoisovalerylurea



M.m. 223.08

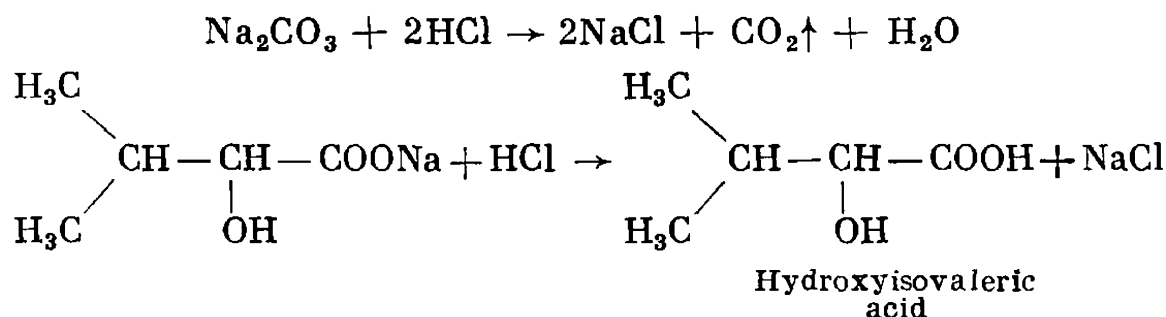
Bromisoval (bromeval, bromurea, bromvaletone) is an acyclic ureide formed by the monobasic monobromoisovaleric acid. It is prepared synthetically from isovaleric acid.

Bromisoval is a white crystalline powder with a bitterish taste and a weak odour. It dissolves very sparingly in water, but is soluble in 95% alcohol. Its melting point is 145-150 °C. Being an ureide, bromisoval is decomposed by an alkali (NaOH) when heated with the formation of ammonia, sodium carbonate, sodium hydroxyisovalerate, and sodium bromide:



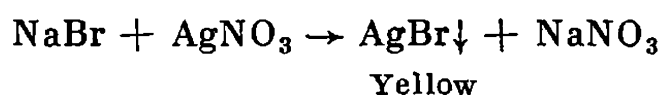
When the products are acidified with dilute hydrochloric acid, gas bubbles (CO₂) evolve, while with subsequent heating, a smell of

hydroxyisovaleric acid is felt:

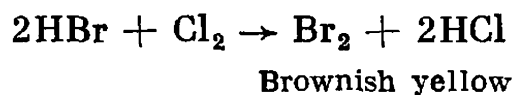
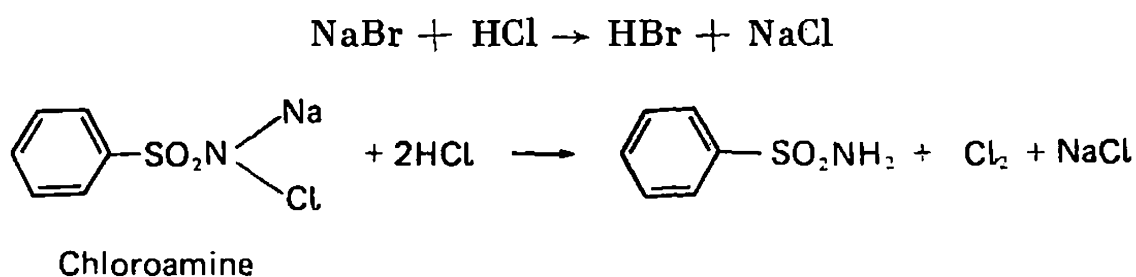


When the drug is heated with an alkali, the organically bound bromine in the bromisoval molecule becomes detached and passes over into the ionogenic state in NaBr. The latter can be confirmed by two reactions:

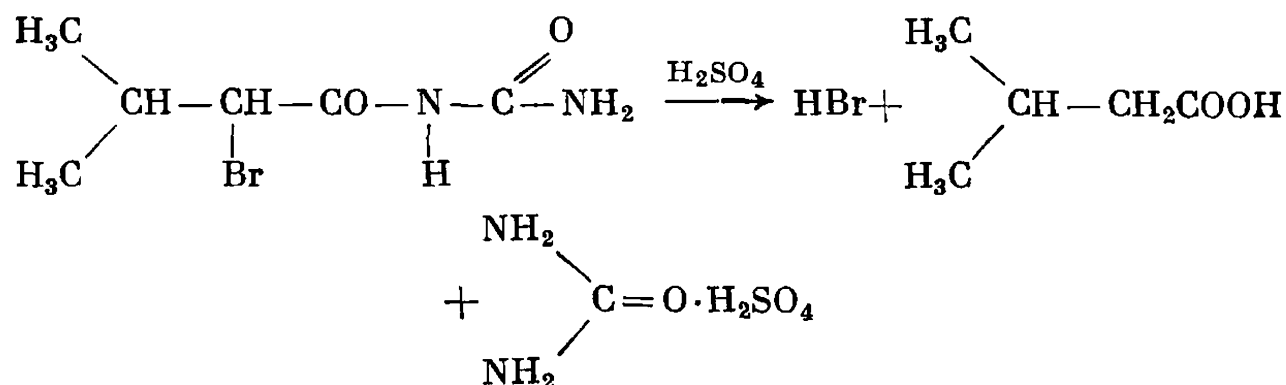
(a) with a silver nitrate solution that precipitates silver bromide:



(b) with an oxidizing agent such as chloroamine in the presence of a mineral acid, for example, HCl. The ionogenic bromine (HBr) is oxidized to molecular bromine which, when chloroform is added, colours it yellow:



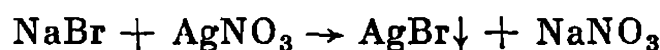
When the drug is heated with concentrated sulphuric acid, the odour of isovaleric acid is felt:



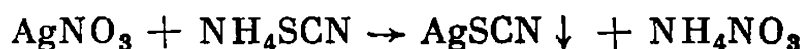
The State Pharmacopoeia recommends all these reactions for identifying the drug.

The content of bromisoval in the drug is determined by finding its bromine content. The drug is heated with an alkali (NaOH) to

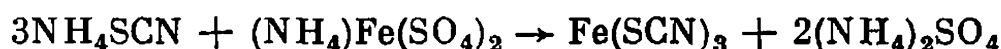
transfer the organically bound bromine into the ionogenic element (NaBr), after which it is determined argentometrically using the Volhard method in the presence of ammonium iron alum:



Yellow



White



Red

Bromisoval has a tranquilizing and soporific action on an organism. It is dispensed in 0.3-g powders and tablets. As a soporific, it is taken in doses of 0.3-0.5 g before sleep, and as a tranquilizer in doses of 0.2-0.3 g two or three times a day. It is listed in Group B.

REVIEW QUESTIONS

1. Which compounds are called urethanes and which are called ureides?
2. What is the reaction of identification of meprotran based on?
3. What reaction underlies the quantitative analysis of meprotran?
4. Can the presence of bromine in bromisoval be proved analytically (without decomposing the molecule)?
5. What is the pharmacological action of bromisoval?

PRACTICAL LESSON

Analysis of Bromisoval

1. Perform an identification reaction.

Boil a small amount of bromisoval with an alkali solution for several minutes and you will feel a smell of ammonia. Cool the solution, acidify it with hydrochloric acid, add a few drops of a chloroamine solution and 1 ml of chloroform, and agitate the mixture. The chloroform layer acquires an orange colour. What causes the colour to appear? Write the equations of the chemical reactions.

2. Conduct a quantitative determination (using argentometry by the Volhard method).

Transfer 0.05 g of the drug into a heat-resistant flask, add 5 ml of a 1 *N* alkali solution, 20 ml of distilled water, cover the flask with a funnel, and heat the mixture during 10 minutes. Next cool the mixture, add 20 ml of a 2 *N* solution of nitric acid and 10 ml of a 0.02 *N* solution of silver nitrate (from a burette), six drops of the ammonium iron alum indicator, and the excess of the 0.02 *N* solution of silver nitrate; titrate with a 0.02 *N* ammonium thiocyanide solution until a flesh-coloured precipitate forms. Write the equations of the chemical reactions.

3. Calculate the content of bromisoval in the drug in per cent by the following formula, derived from formula (1.1):

$$X = \frac{(V_0 K_0 - VK) T}{a} \times 100 = \frac{(10.0 K_0 - VK) \times 0.004462}{0.05} \times 100$$

where V_0 is the volume of the 0.02 *N* silver nitrate solution, ml, V is the volume of the 0.02 *N* ammonium thiocyanide solution, ml, K_0 is the correction factor

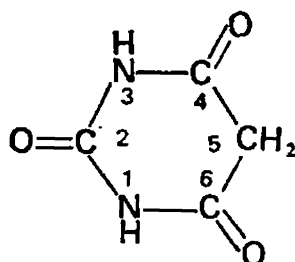
for the 0.02 *N* silver nitrate solution, *K* is the same for the 0.02 *N* ammonium thiocyanide solution, $T = 0.004\ 462$ g/ml, and *a* is the mass of the sample, g.

The State Pharmacopoeia requires that the content of $C_6H_4BrN_2O_2$ be at least 97.5%.

4. Arrive at a conclusion whether the analysed drug meets the requirements of the State Pharmacopoeia.

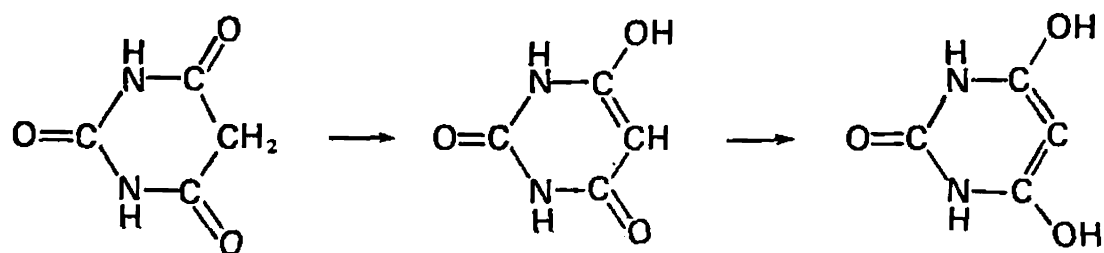
Chapter 18. Cyclic Ureides (Barbituric Acid Derivatives)

Barbituric acid is a cyclic ureide—a product of condensation of urea with dibasic malonic acid:

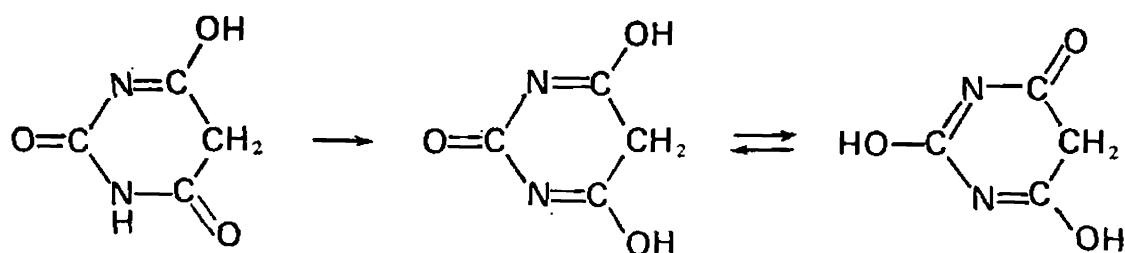


Its acidic properties are due to the hydrogens of the methylene ($-CH_2$) and imide ($\begin{smallmatrix} & \diagup & \\ & N & \\ & \diagdown & \end{smallmatrix}NH$) groups, which can be substituted by

metals with the formation of salts. Barbituric acid exists in two tautomeric forms:



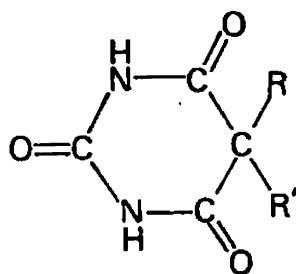
Keto-enol tautomerism



Imido-imidol tautomerism

The imido-imidol tautomerism is generally a feature of barbituric acid derivatives in which the hydrogens of the methylene group are

substituted by radicals:



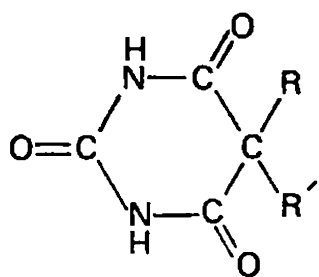
The hydrogens of the enol groups (—OH) exhibit acidic properties and can be substituted by metals with the formation of salts.

Barbituric acid is not a medicament by itself, but it can yield an enormous number of drugs most of which are obtained by substituting various radicals for the hydrogens of the methylene group (Table 2).

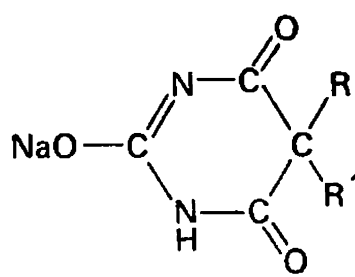
In this connection, a very large number of therapeutically active drugs have been developed, chiefly with a soporific action. Some barbiturates in addition to their soporific effect exhibit an anticonvulsive action (phenobarbital), while others are administered as narcotics [hexenal (hexobarbital)].

The barbiturates differ from one another in the nature of the radicals in the methylene group (R and R') and in the nature of the substituents at N_1 and N_3 .

The barbiturate drugs are produced either in the form of the sodium (monosubstituted) salts (barbital sodium, barbamy, ethaminal sodium, hexenal) or in the acid form (barbital, phenobarbital):



Acid form



Salt form

Thiobarbiturates also exist in which the oxygen in the second position of the ring has been replaced by sulphur, for example, thiopental sodium (penthiobarbital, thiopentone):

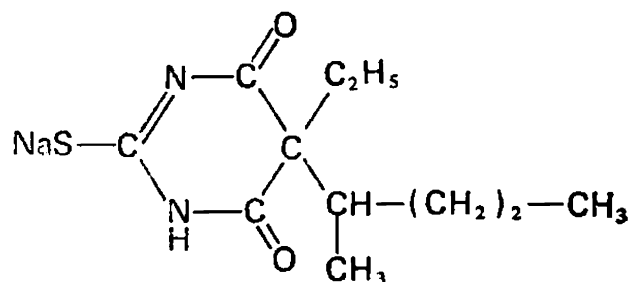


TABLE 2. Drugs of the Barbiturate Group

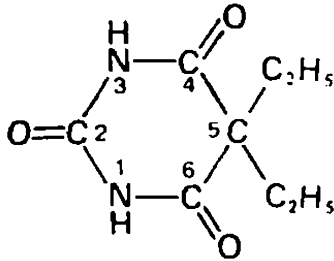
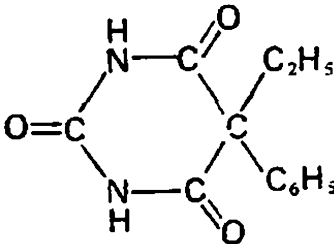
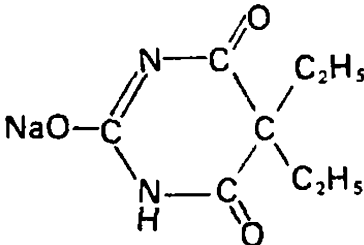
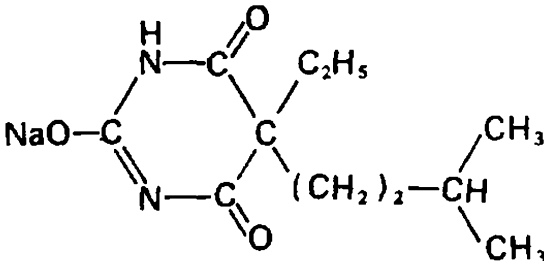
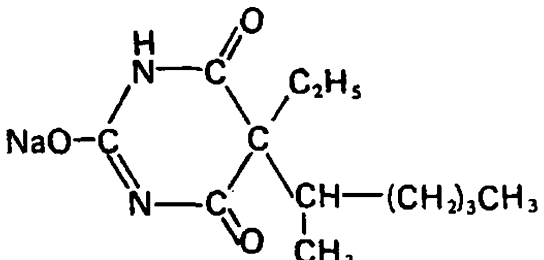
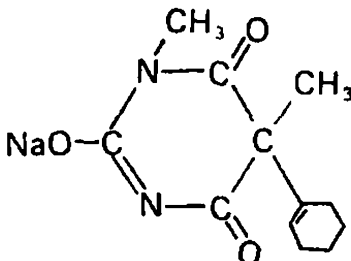
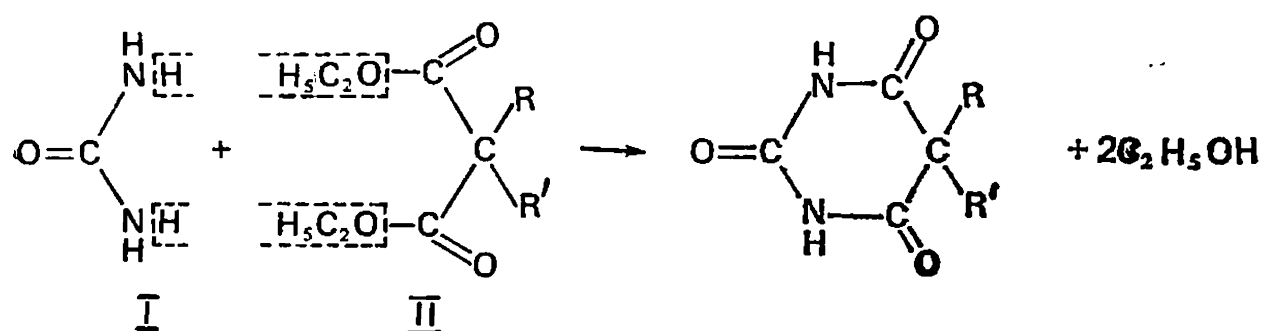
Name	Structural formula and chemical name
Barbital (<i>Barbitalum</i>) (barbitone) M.m. 184.20	 5,5-Diethylbarbituric acid
Phenobarbital (<i>Phenobarbitalum</i>) (phenobarbitone, phenemal) M.m. 232.24	 5-Ethyl-5-phenylbarbituric acid
Barbital sodium (<i>Barbitalum natrium</i>) M.m. 206.18	 Sodium 5,5-diethylbarbiturate
Barbamyl (<i>Barbamylum</i>) (amobarbital, pentymal) M.m. 248.26	 Sodium 5-ethyl-5-isoamylbarbiturate
Ethaminal sodium (<i>Aethaminalum natrium</i>) (Pentobarbital sodium) M.m. 262.29	 Sodium 5-ethyl-5(2-amyl)barbiturate
Hexenal (<i>Hexenalum</i>) (hexobarbital, methylcyclobarbital) M.m. 258.25	 Sodium 1,5-dimethyl-5-(cyclohexene-1-yl)barbiturate

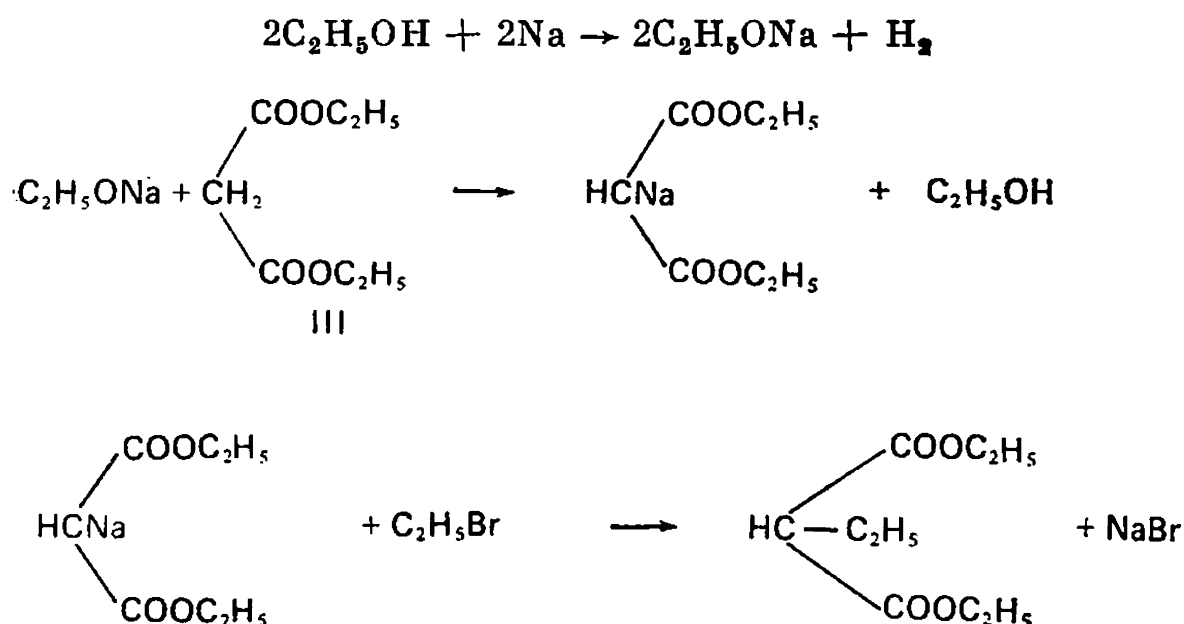
Table 2 gives the chemical structure of barbiturate salts and acids that are pharmacopoeial drugs.

Since the barbiturates mainly differ from one another in the nature of the radicals (R, R'), while the remaining part of their molecule is the same, their physical and chemical properties, ways of production, and methods of analysis are similar.

The method of producing barbiturates consists in condensing urea (I) with the diethyl ester of dialkylmalonic acid (II):

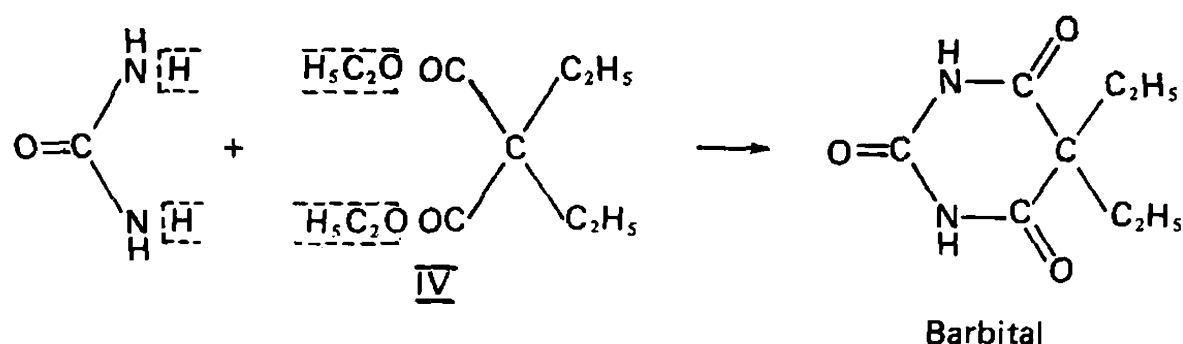


The malonic acid is taken in the form of an ester because the free acid can easily become decarboxylated, and no cyclic ureide may form. First the corresponding radicals are introduced into the diethyl ester of malonic acid by one of the chemical methods of organic chemistry, for example, by the action of metallic sodium and the relevant alkyl bromide. When producing barbital, where R and R' are ethyl (C₂H₅), the reaction proceeds as follows:



Next, the operation is repeated, the second hydrogen of the methylene group is substituted by an ethyl radical, and the diethyl ester

of diethylmalonic acid (IV) is obtained, which is condensed with urea:



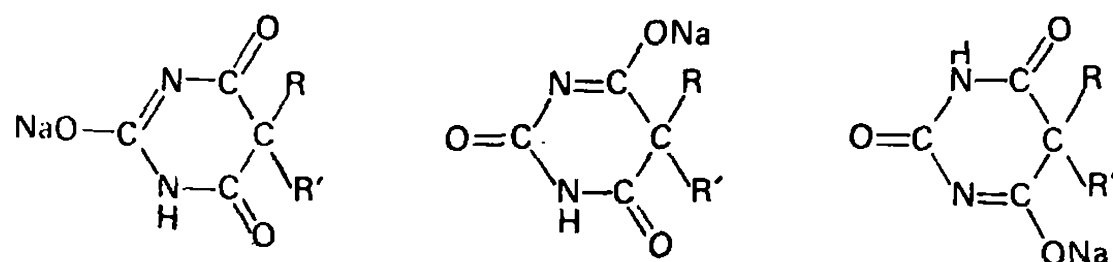
Depending on the nature of the radicals, different variants of synthesis can exist for each barbiturate.

The barbiturates are finely crystalline white powders*. The acid forms of the barbiturates (barbital, phenobarbital) are sparingly soluble in water, but are soluble in organic solvents, solutions of alkalies and carbonates. The salt forms of the barbiturates dissolve well in water.

The following identification reactions are used for barbiturates:

1. With alkalies, the barbiturates form only monosubstituted salts. The disubstituted salts hydrolyze so readily that they do not virtually exist.

Hydrogen can be replaced by a metal in positions 2, 4, and 6:

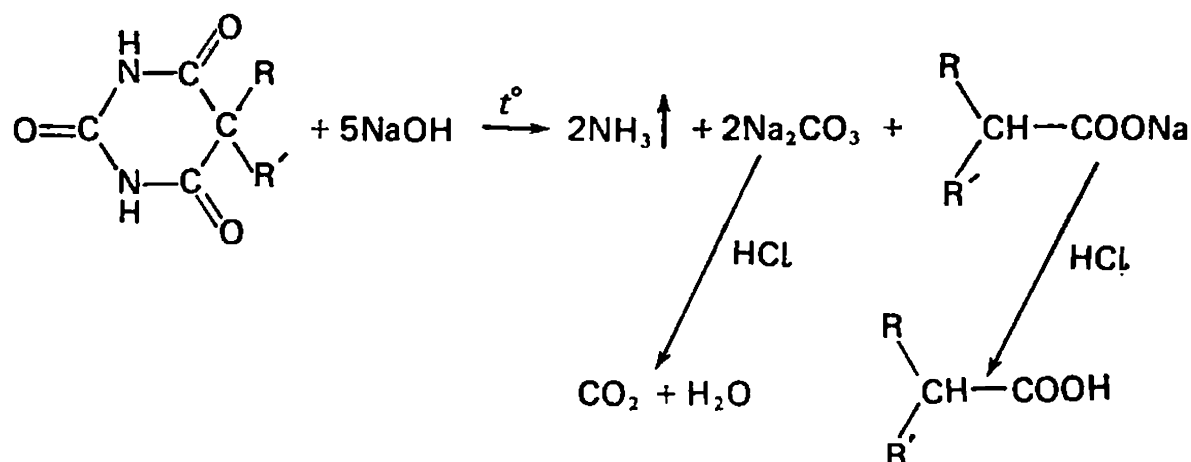


2. The barbiturates can enter into a reaction with salts of the heavy metals (AgNO_3 , CuSO_4 , CoCl_2 , etc.) with the formation of complexes. All the barbiturates form a complex of a blue-violet colour with a solution of cobalt nitrate $\text{Co}(\text{NO}_3)_2$ in the presence of calcium chloride. Hence, this reaction is common for all barbiturates and is a pharmacopoeial one.

3. A reaction of fusing barbiturates with a solid alkali (for example, NaOH) is also a common one because regardless of the nature of the barbiturate, the decomposition products are ammonia, sodium carbonate, and sodium dialkylacetate. When the reaction mixture is

* Hexenal, unlike the other barbiturates, is a white foamy mass. It decomposes in the air under the influence of carbon dioxide. Hexenal, ethaminal sodium, and barbamyl are hygroscopic, which must be taken into consideration when storing them.

acidified, gas bubbles (CO_2) evolve, and an odour of the dialkylacetic acid is felt:



The specific reactions for the barbiturates are chiefly determined by the nature of the radicals. For example, when barbiturates with a phenyl nucleus as one of the radicals (phenobarbital) or a cyclohexenyl ring (hexenal) are heated with formalin and concentrated sulphuric acid, a pink ring forms at the interface of the two media (phenobarbital) or a brownish-red ring with a greenish fluorescence (hexenal). This reaction is recommended by the State Pharmacopoeia to identify these drugs.

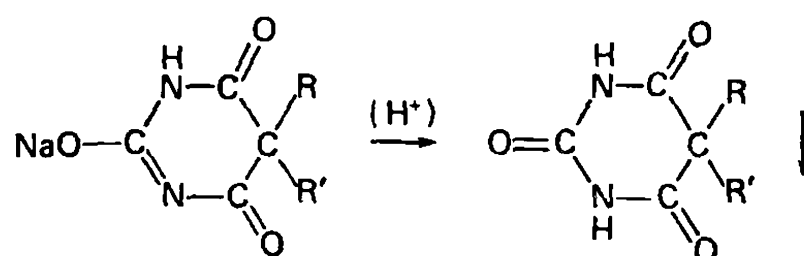
To distinguish one barbiturate from another one, the State Pharmacopoeia recommends reactions with salts of heavy metals, namely, with copper sulphate in the presence of a hydrogen carbonate buffer (a mixture of Na_2CO_3 and NaHCO_3 in definite proportions). Depending on the nature of the barbiturate, the colour of the formed complex varies (Table 3).

TABLE 3. Identification Reactions for Selected Barbiturates with Copper Sulphate

Name	Result of reaction with copper sulphate solution
Barbital	Blue colour, next a reddish-lilac precipitate appears
Barbamyl (amobarbital)	A pinkish-lilac precipitate; it does not change when left in the air
Hexenal (hexobarbital)	Light blue colour changing to bright blue; a white precipitate appears
Phenobarbital	A pale lilac precipitate appears; it does not change when left standing
Ethaminal sodium (pentobarbital sodium)	A light blue precipitate

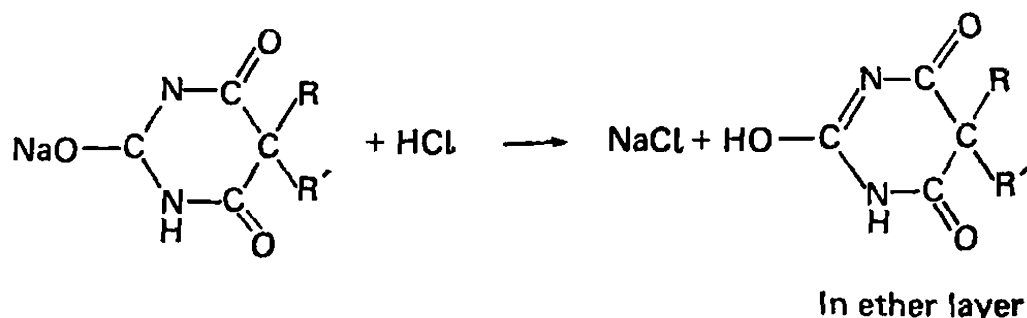
The acid forms of the barbiturates are determined by their melting point, which is quite definite for each barbiturate.

The sodium salts of the barbiturates (hexenal, barbamy, barbital sodium, ethaminal sodium) when reacted with mineral acids evolve the acid forms of the relevant barbiturates, which precipitate. After drying of the precipitate, the melting point of the relevant acid is determined. This reaction is the official one for identifying barbiturate salts and distinguishing them from one another:



The methods of the quantitative determination of the barbiturates are based on their chemical properties. Since barbiturates exhibit acidic properties, while their sodium salts readily hydrolyze with the formation of an alkali, the chief method of the quantitative determination is that of neutralization.

The barbiturate salts (barbital sodium, ethaminal sodium, barbamy, hexenal) are titrated with an acid using methyl orange or methyl red as an indicator in the presence of ether. The latter extracts the acid formed during titration:



The acid forms of the barbiturates (barbital, phenobarbital) are determined quantitatively by acid-base titration in non-aqueous media because their dissociation constant in aqueous solutions is low, and they are weak acids.

A 0.1 *N* solution of sodium hydroxide in a mixture of methanol and benzene or sodium methylate is the titrant in this case.

Dimethylformamide $\text{HCON} \begin{matrix} \text{CH}_3 \\ \text{CH}_3 \end{matrix}$ is the non-aqueous solvent, and thymol blue or phenolphthalein is the indicator. The method is a pharmacopoeial one.

Other methods are also used for the quantitative determination of the salt and acid forms of the barbiturates that are based on the chemical properties of these compounds.

The physiological activity of the barbiturates depends on the chemical structure of their molecules and mainly on the nature of the radicals.

Amplification of the soporific action of drugs of this group depends on a number of factors:

(1) with an increase in the number of carbon atoms in the chain to five or six, the soporific effect grows; a further increase in the number of carbon atoms in the chain results in a drop in the physiological activity and in the appearance of convulsions;

(2) a phenyl radical simultaneously present with an ethyl one increases the soporific effect and imparts an anticonvulsive action to the drug;

(3) a branched chain of the radical amplifies the soporific action, but the duration of action of the drug is reduced;

(4) an unsaturated bond, a halogen in the barbiturate molecule, or their simultaneous presence increases the soporific effect;

(5) when the hydrogens of the imide groups in position 1 or 3 are substituted by various alkyls, the duration of action of the drug diminishes and it acts as a stimulant.

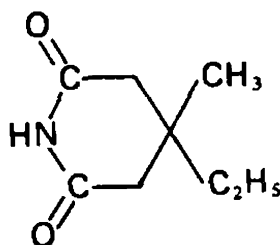
With the simultaneous substitution of the imide group hydrogens in positions 1 and 3, the drug may cause convulsions.

Barbiturates are dispensed in powders and tablets. Hexenal is dispensed in glass bottles (1 g) hermetically sealed with rubber stoppers pressed down by aluminium caps. Solutions of hexenal for intravenous narcosis are prepared using a physiological saline solution under aseptic conditions prior to administration.

The drugs should be stored in well closed containers. Hygroscopic drugs should be kept in a dry, cool place protected from light. All barbiturates are listed in Group B.

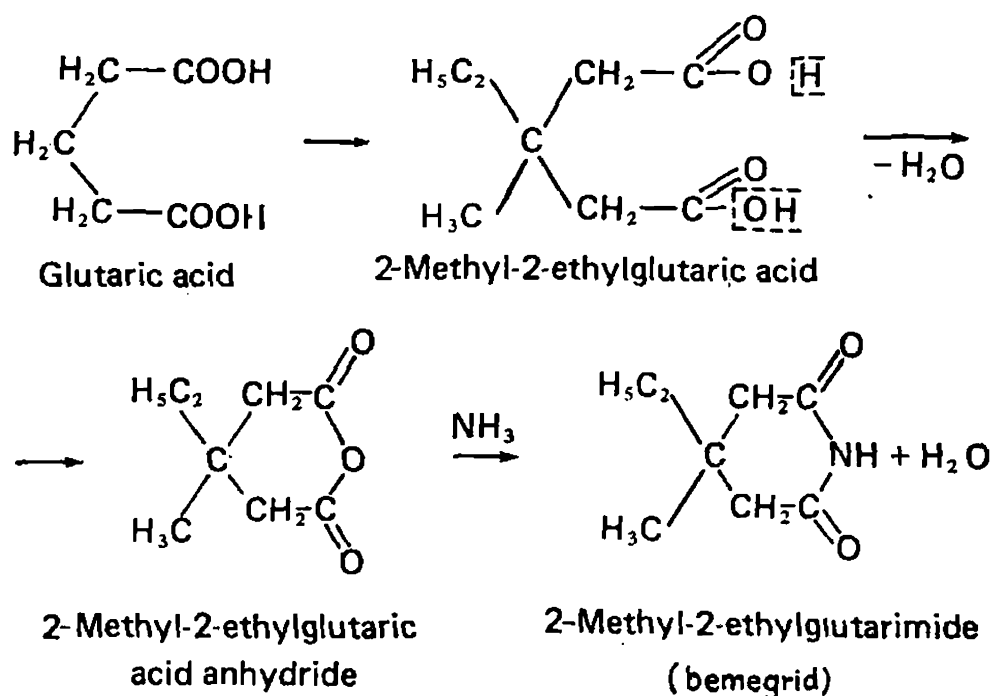
When barbiturates are taken for prolonged periods and in increased doses, they may cause poisoning, therefore their use must be controlled by a doctor. For a long time, medicine did not have sufficiently effective drugs for treating poisoning by barbiturates. Generally stimulators of the central nervous system such as strychnine and corazol were employed for this purpose.

It was later established that 2-ethyl-2-methylglutarimide, named bemegride, is a specific antagonist of barbiturates. The drug is a pharmacopoeial one.

Bemegride (*Bemegridum*)*2-Ethyl-2-methylglutarimide* $C_8H_{13}NO_2$

M.m. 155.20

In its structure, bemegride is an imide of substituted dicarboxylic glutaric acid. The preparation of this drug can be depicted schematically as follows:



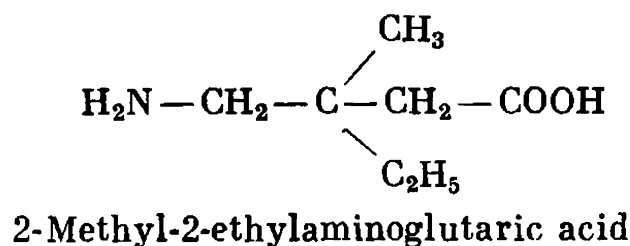
Bemegride is a white crystalline odourless powder with a bitter taste. It dissolves sparingly in water and ether, and very sparingly in 95% alcohol.

The State Pharmacopoeia recommends the following identification reactions:

(a) a condensation reaction with vanillin in an acidic medium; the condensation product acquires a cherry-red colour that turns to blue-violet;

(b) a reaction with ninhydrin; the drug is first treated with bromine water in the presence of sodium hydroxide. The hypobromide NaBrO resulting from the reaction of the bromine with the alkali facilitates the transformation of the glutaric acid imide (bemegride) into aminoglutaric acid (substituted 3-aminobutyric acid), and the

latter is exactly what is determined by the reaction with ninhydrin (see the reactions of identification of glutaminic acid, p. 184):



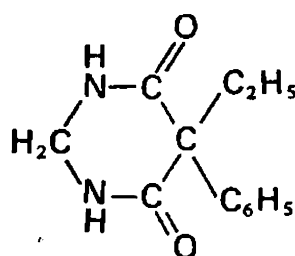
The content of the drug is determined with respect to the nitrogen by the Kjeldahl method.

Bemegride is dispensed in ampoules containing 10 ml of a 0.5% sterile solution in an isotonic sodium chloride solution and in hermetically sealed bottles containing 30 or 100 ml of such a solution. The drug is listed in Group B.

The drug hexamidine, which is described in the State Pharmacopoeia, is close in its structure to barbiturates and, particularly, to phenobarbital.

Hexamidine (*Hexamidinum*)

5-Ethyl-5-phenylhexahydropyrimidinedione-4,6



$\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_2$

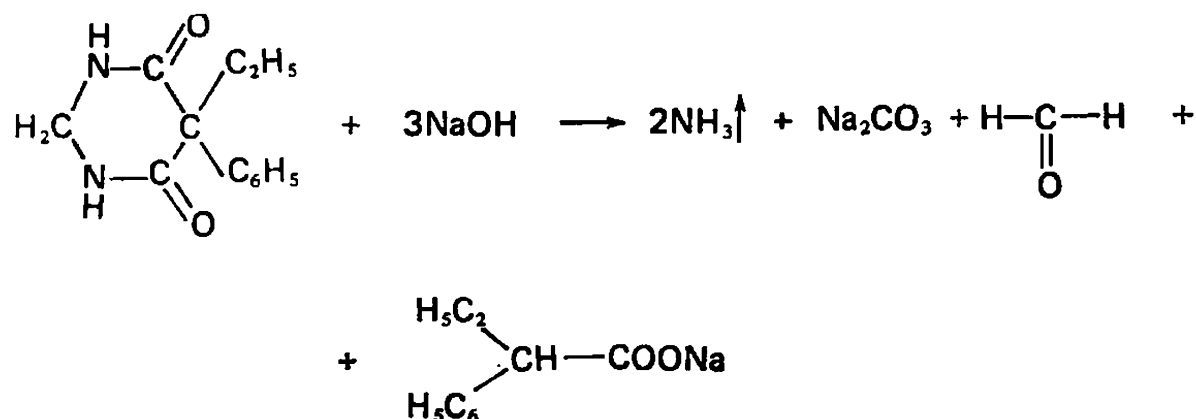
M.m. 218.25

Hexamidine differs from phenobarbital in its chemical structure in that the group $>\text{C}=\text{O}$ in position 2 is substituted by a methylene group ($>\text{CH}_2$). This is why hexamidine is not an ureide (barbiturate) and therefore does not exhibit a pronounced soporific effect. But, since there are an ethyl and a phenyl radicals in position 5, similar to phenobarbital, it has an anticonvulsive action.

Hexamidine is a white odourless crystalline powder. It is insoluble in water, ether, and benzene, and is sparingly soluble in 95% alcohol and acetone. Its melting point is 280-284 °C.

The State Pharmacopoeia proposes the following identification reactions: (a) the detection of ammonia by red litmus paper turning

blue after fusion of the drug with a crystalline alkali (NaOH):



(b) when the drug is heated with disodium chromotropate in the presence of concentrated sulphuric acid, a lilac colour forms (the product of condensation of the evolved formaldehyde with chromotropic acid). The sulphuric acid performs two functions in this reaction, namely, it is a dehydrating agent in the condensation of the formaldehyde with the chromotropic acid, and an oxidizing agent which is reduced in the reaction to sulphurous acid (see the reaction of identification of formaldehyde, p. 171).

The content of the drug is determined with respect to the nitrogen by the Kjeldahl method.

The drug is dispensed in 0.125- and 0.25-g powders and tablets. It should be stored in well closed containers. It is listed in Group B.

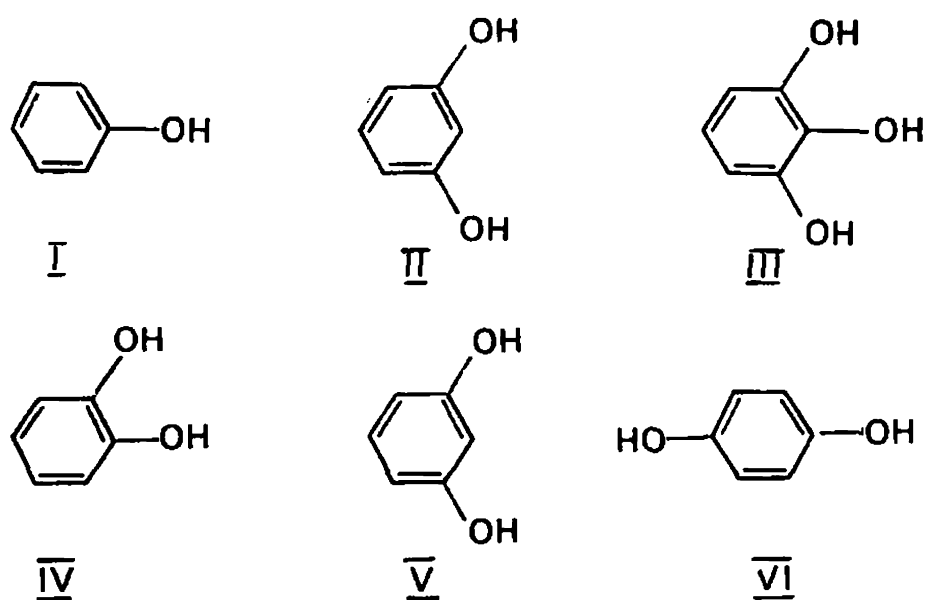
REVIEW QUESTIONS

1. Which compounds are called cyclic ureides?
2. How is barbituric acid formed?
3. Name each functional group of barbituric acid: $-\text{NH}$, $> \text{C} = \text{O}$, and $\text{H}_2\text{C} <$.
4. What forms of barbituric acid are possible?
5. Which form is responsible for the acidic properties?
6. Why is a malonate used in the synthesis of barbital instead of malonic acid?
7. What process occurs between copper salts and barbiturates?
8. Why is the quantitative determination of barbital conducted in an alcohol medium?
9. What are the acidic properties of barbituric acid due to?
10. What underlies the ketoenol and imido-imidol tautomerism of barbituric acid?
11. Why do the acid forms of barbiturates readily dissolve in alkalies?
12. Why are the sodium salts of barbiturates unstable in storage?
13. What explains the ability of barbiturates to form complexes?
14. Will barbiturates react with alkaloids and why?
15. Compare the pharmacological action of all the barbiturates. Give a chemical substantiation of the change in their pharmacological properties and note the dependence of the pharmacological action on the introduction of various radicals into a molecule.

Chapter 19. Phenols

Phenols belong to the aromatic compounds. They are derivatives of benzene in whose molecule one or more hydrogen atoms are replaced by hydroxyl. Depending on the number of hydroxyl groups in a molecule, phenols are divided into monatomic (I), diatomic (II), and triatomic (III) compounds.

Di- and triatomic phenols can have different isomers depending on the position of the phenol hydroxyls in the ring. For example, diatomic phenols exist in three isomeric forms: *ortho*-dihydroxybenzene or pyrocatechol (IV), *meta*-dihydroxybenzene or resorcinol (V), and *para*-dihydroxybenzene or hydroquinone (VI):



Phenols are produced both from natural sources and synthetically. The main natural source of phenols is coal tar formed in the dry distillation of wood and in a large amount in the dry distillation of coal.

The coal tar is subjected to fractional distillation, and the fraction boiling within 170-250 °C yields phenol and a number of its homologues. Some phenols are a constituent part of various natural resins and tannins. Examples are resorcinol, pyrocatechol, and phloroglucinol. Other phenols and their derivatives are encountered in the essential oils of various plants.

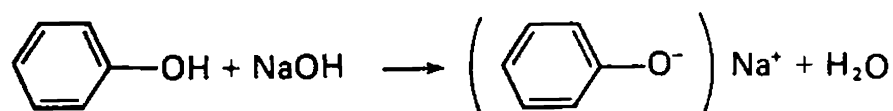
However, the natural sources far from satisfy the demand for phenols, therefore a substantial amount of them is produced synthetically. Fusion of salts of benzene sulphoacids with alkalies is used the most.

The majority of the phenols are crystalline substances with a strong characteristic odour. The monatomic phenols dissolve poorly in water. Unlike them, the diatomic phenols dissolve in water. Pure phenols are colourless, but owing to their rapid oxidation (especially

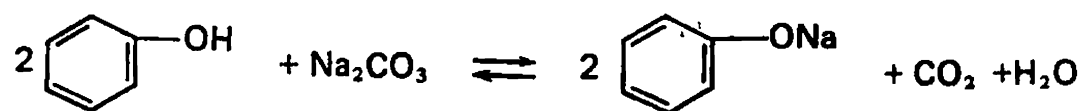
diatomic phenols), they turn pink in the air, while in prolonged storage they turn brown.

The chemical properties and identification reactions of the phenols are due, on the one hand, to the functional group—the phenol hydroxyl, and on the other, to the aromatic ring itself:

(1) unlike alcohols, phenols have the nature of weak acids. They dissolve in an aqueous solution of alkalis, for example, NaOH, to form phenolates (salts), which confirms their acidic nature:

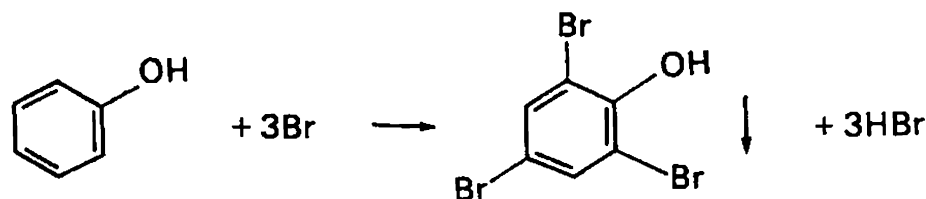


But their acidic nature is so weak that even such a weak acid as carbonic acid displaces phenols from their salts (phenolates). This is why phenols can dissolve in alkalis, but cannot dissolve in carbonates, because the formed carbonic acid immediately decomposes the phenolate. This property of phenols distinguishes them from acids:



(2) phenols are characterized by substitution reactions due to the presence of an aromatic ring. The hydrogen atoms in a phenol molecule in the ortho- and para-positions relative to the phenol hydroxyl can be substituted by halogens, a nitro group, sulpho group, and other substituents. These reactions proceed with phenols much more readily than with benzene.

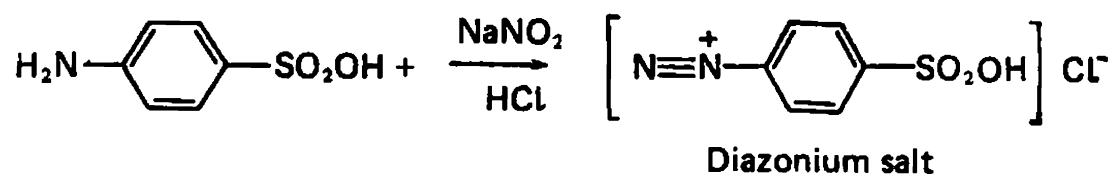
Phenols and their salts can be readily nitrated (the nitrocompounds are coloured yellow) and brominated (the bromine derivatives of the phenols are insoluble and precipitate). This property is used in pharmaceutical analysis:



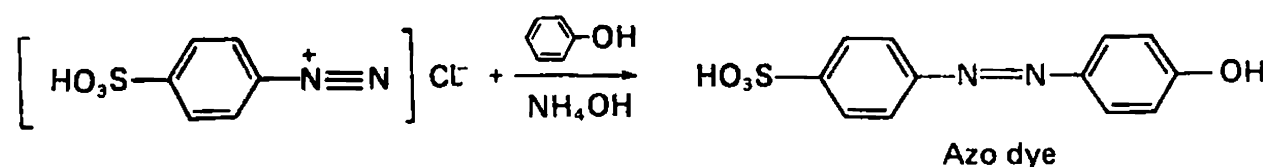
(3) phenols readily enter into condensation reactions with aldehydes. The reaction of phenols with formaldehyde in the presence of sulphuric acid proceeds with the formation of coloured products (aurine dyes), which is used to confirm the presence of compounds of a phenolic nature;

(4) phenols readily combine with diazonium salts in an alkaline medium to form azo dyes. The coupling occurs in the ortho- and para-positions relative to the phenol hydroxyl. Generally a 0.1% solution of sulphanilic acid and a 1% solution of sodium nitrite in

an acidic medium are used as the reagent:

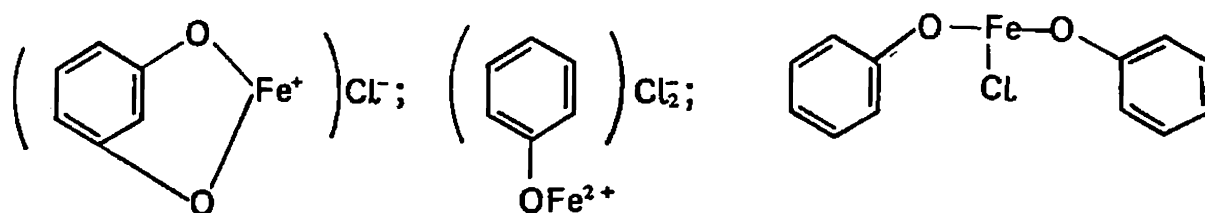


The formed diazonium salt becomes coloured when a compound having a phenolic nature and a few drops of an ammonia solution are added owing to the formation of an azo dye:

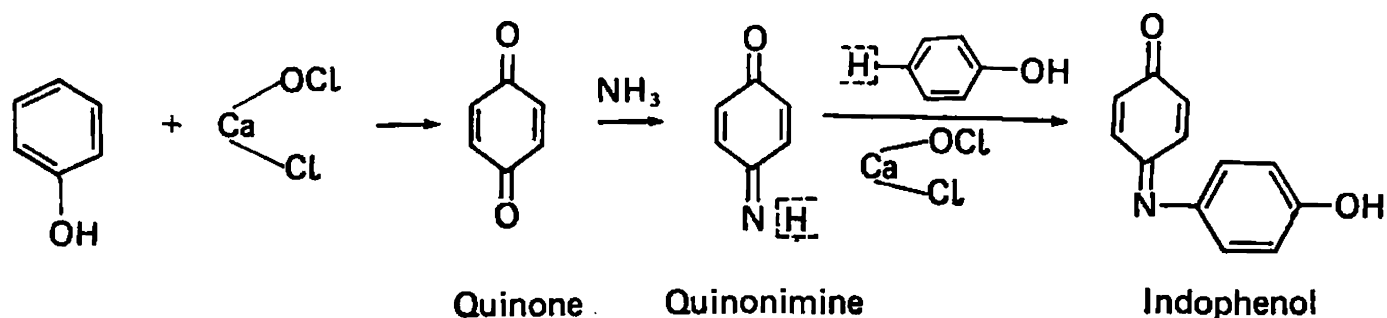


(5) phenols can readily be oxidized and yield complexes with salts of the heavy metals, of which iron(III) chloride is used the most. The colour of the complexes with iron(III) chloride depends on the number and arrangement of the phenol hydroxyl groups in a molecule. For example, monatomic phenols are generally coloured blue or violet. Diatomic phenols are coloured, depending on the arrangement of the hydroxyl groups in a molecule: green (pyrocatechol), blue (resorcinol), or green transforming into yellow (hydroquinone).

The complexes formed can vary in structure:



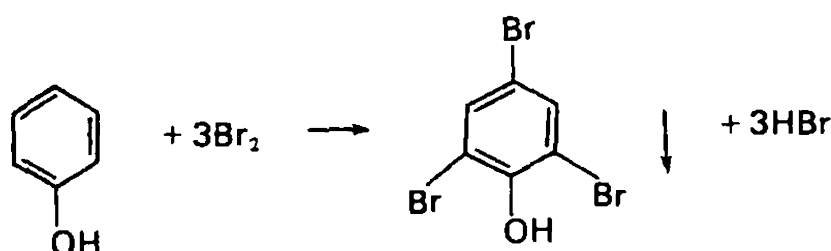
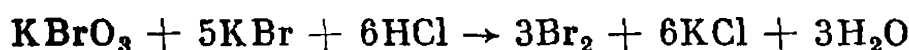
The formation of coloured indophenols (the indophenol test) is based on the ability of phenols to become readily oxidized. A phenol compound is subjected to the action of an oxidizing agent (bromine water, chlorinated lime, etc.) and ammonia. The product is blue indophenol:



All the above reactions are employed for identifying drugs containing a phenol hydroxyl group in their molecule.

At present, volumetric methods are chiefly used for the quantitative determination of phenols, although recent years have seen the

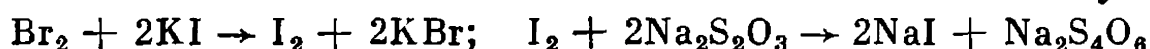
appearance of some physicochemical methods. The most widespread of the volumetric methods is the bromatometric one, which has been adopted by the State Pharmacopoeia. When the phenol being studied is reacted with a bromate-bromide mixture, the phenol becomes brominated with the formation of tribromophenol:



Two procedures can be used for the quantitative determination of phenols with the aid of a potassium bromate solution:

(1) direct titration: the analyte phenol solution is acidified, potassium bromide is added, and the mixture is then titrated with a potassium bromate solution until the yellow colour characteristic of an excess of bromine in the reaction disappears. Generally methyl orange is used as the indicator in this case. It becomes decolourized at the equivalence point owing to the excess bromine;

(2) back-titration: potassium bromide, an acid, and an excess of a titrated potassium bromate solution are added to the analyte phenol solution. The excess of bromine is determined iodimetrically:

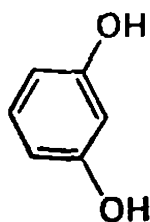


Phenols are employed as antiseptics. Their antiseptic action is based on their ability to coagulate proteins. Phenols also have a bactericidal action, i.e. are capable of killing microorganisms or produce conditions that are unfavourable for their vital activities.

Since phenols are easily oxidized, it is recommended to store drugs containing them in well closed dark glass jars or bottles sealed with paraffin wax.

Resorcinol (*Resorcinum*)

meta-Dihydroxybenzene



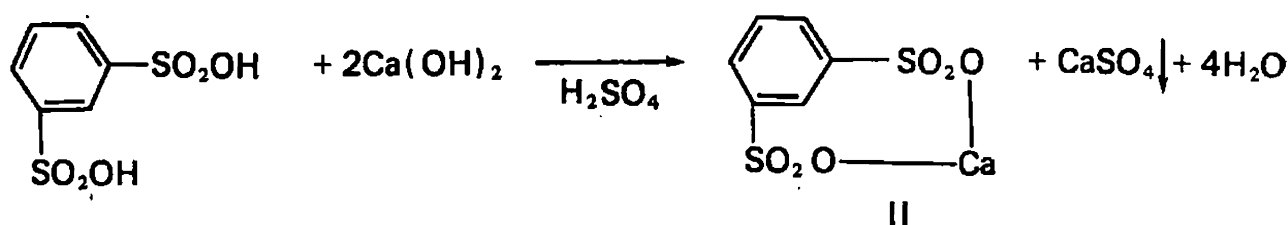
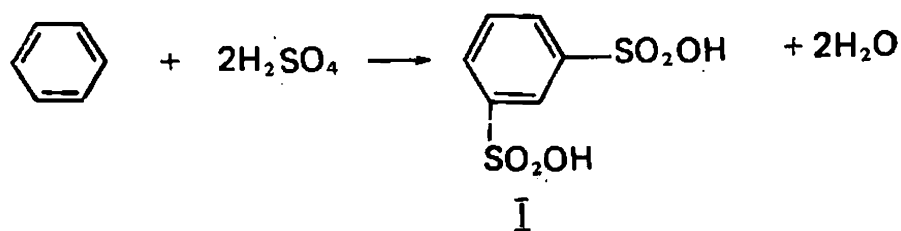
$\text{C}_6\text{H}_6\text{O}_2$

M.m. 110.11

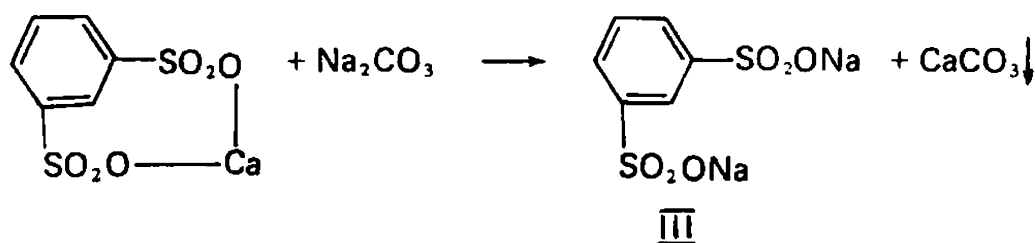
Resorcinol is a diatomic phenol. It forms colourless or slightly pink or yellow acicular crystals or a crystalline powder. Sometimes the colour of the crystals is almost brown. This is due to the improper storage of the resorcinol, which oxidizes very readily. Unlike the

other phenols, resorcinol dissolves easily in water, alcohol, and ether. It is soluble in fatty oil and glycerin. It dissolves sparingly in chloroform. When heated, it evaporates completely.

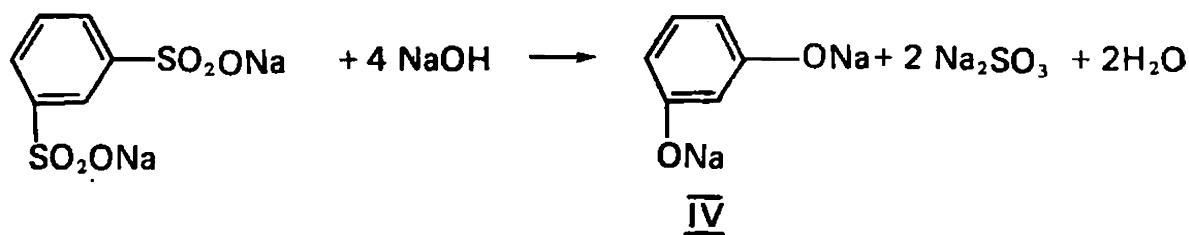
Resorcinol is a constituent part of many resins and tannins, but it is produced synthetically from benzene by sulphonation and fusion with an alkali. Benzene is treated with concentrated sulphuric acid, the product being benzene *meta*-disulphonic acid (I). Next the reaction mixture is treated with lime. The sulphoacid under these conditions forms a calcium salt (II) soluble in water, while the excess sulphuric acid is removed in the form of calcium sulphate:



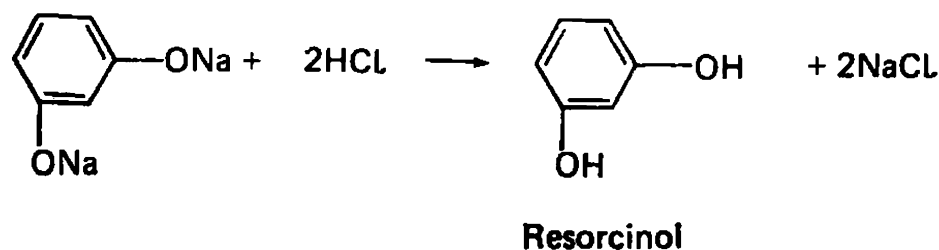
Next the solution containing the calcium salt of benzene *meta*-disulphonic acid (II) is treated with sodium carbonate:



The formed disodium salt of benzene *meta*-disulphonic acid (III) is fused with sodium hydroxide at 320-350 °C:



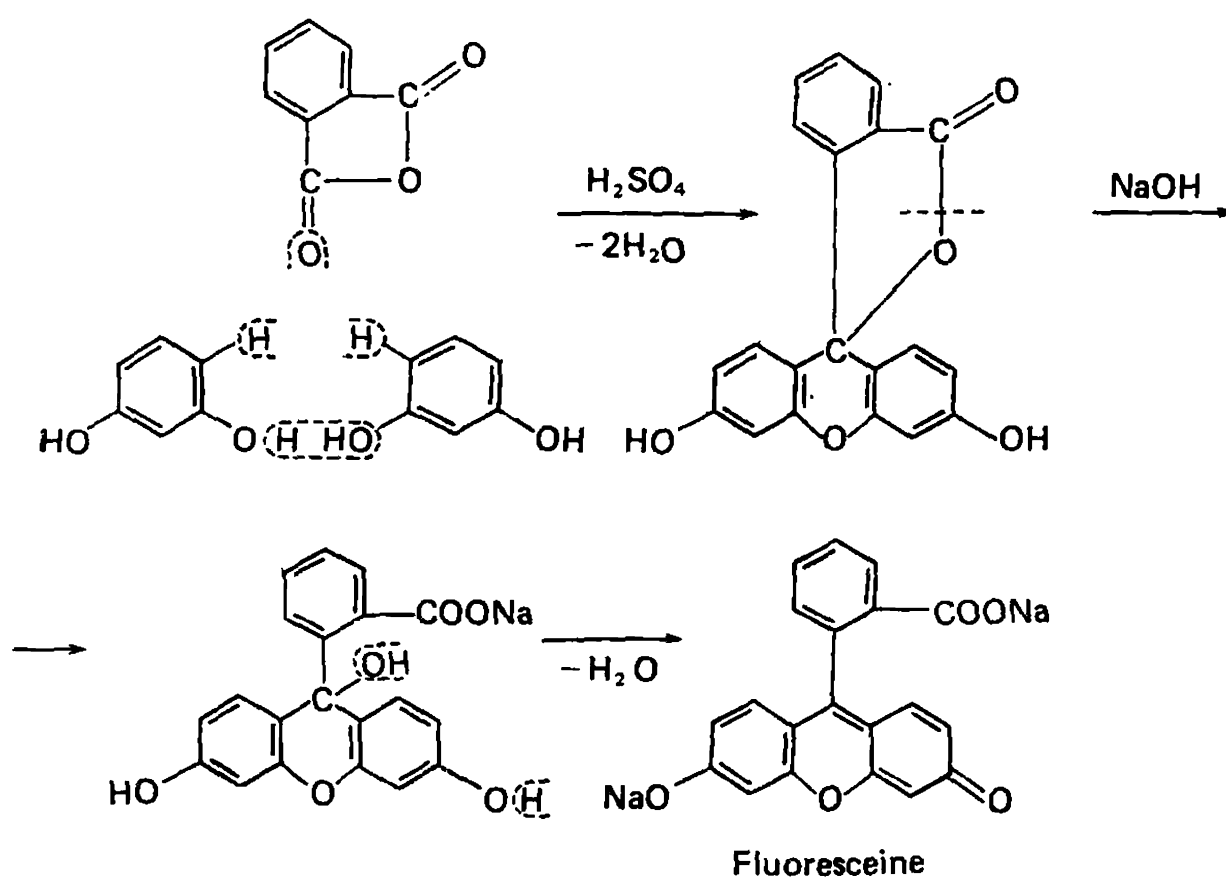
The obtained resorcinate is dissolved in water and treated with a strong acid, for example, HCl, and resorcinol is produced:



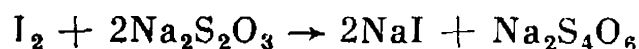
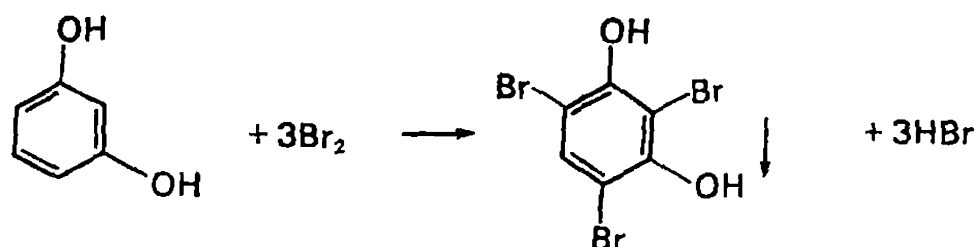
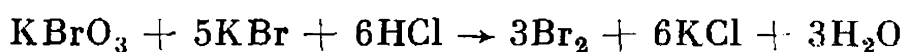
The resorcinol is purified by distillation.

Resorcinol, like the other phenols, is readily oxidized and is itself a reducing agent. It can reduce silver from an ammonia solution of silver nitrate.

Resorcinol enters into all the reactions typical of phenols, including a reaction with formalin and sulphuric acid (a red precipitate forms at the bottom of the test tube). A specific reaction for resorcinol distinguishing it from all the other phenols is the reaction of its fusion with phthalic anhydride in the presence of concentrated sulphuric acid and then of NaOH with the formation of fluoresceine—a yellow-red solution with a green fluorescence (the pharmacopoeial reaction):



The content of resorcinol is determined by bromatometry (the pharmacopoeial method):



The antiseptic action of resorcinol is more pronounced than that of monatomic phenol. This is due to its stronger reducing properties, especially in an alkali medium.

Resorcinol is administered externally in skin diseases (eczema, fungous diseases, etc.) in the form of 2-5% aqueous and alcohol solutions and 5-10-20% ointments.

It should be stored in orange glass jars (light stimulates oxidation).

REVIEW QUESTIONS

1. Which compounds are called phenols?
2. How are phenols classified?
3. What pharmacological properties do phenols have and what are they due to?
4. Why do phenols dissolve in alkalis, but fail to dissolve in carbonates?
5. What chemical properties do phenols have?
6. What reactions can be used to identify phenols?
7. What distinguishes direct titration from back-titration used in the bromatometric determination of phenols?
8. What physicochemical methods can be employed for the quantitative determination of phenols?
9. What are the chemical properties of resorcinol?
10. Why is the antiseptic action of resorcinol stronger than that of phenol?
11. Why is resorcinol incompatible with alkalies?
12. Which properties of resorcinol affect its storage?

PRACTICAL LESSON

Analysis of Resorcinol

1. Perform identification reactions:

(a) dissolve a small amount of the analyte powder in water, add one drop of an iron trichloride solution. A blue-violet colour appears that changes to yellow-brown when an ammonium hydroxide solution is added;

(b) fuse about 0.05 g of resorcinol with 0.1 g of phthalic anhydride and one drop of concentrated sulphuric acid. Dissolve the yellow-brown melt obtained in 2 ml of an alkali and dilute the solution with water. A yellow solution with a green fluorescence forms (demonstrated by one student). Write the equations of the chemical reactions.

2. Perform a quantitative determination (by bromatometry).

Transfer a sample of the drug weighing 0.1 g into a 100-ml measuring flask, add water up to the mark, and thoroughly stir the contents. Transfer 10 ml of the diluted solution into a flask for titration, add from a burette 15 ml of a 0.1 *N* potassium bromate solution, 0.2 g of potassium bromide, 10 ml of a 2 *N* sulphuric acid solution, and let the mixture stand for 10 minutes in a dark place. Next add 10 ml of a 5% potassium iodide solution and titrate the evolved iodine with a 0.1 *N* sodium thiosulphate solution until the colour vanishes. Write the equations of the chemical reactions.

3. Calculate the resorcinol content in the drug in per cent by the formula

$$X = \frac{(V_0 K_0 - VK) TV_1}{aV_2} \times 100 = \frac{(15.0 K_0 - VK) \times 0.001835 \times 100}{0.1 \times 10.0} \times 100$$

where V_0 is the volume of the 0.1 *N* potassium bromate solution, ml, V is the volume of the 0.1 *N* sodium thiosulphate solution, ml, K_0 is the correction factor for a standard potassium bromate solution, $T = 0.001\ 835$ g/ml, K is the correction factor for a standard sodium thiosulphate solution, a is the mass of the drug, g, V_1 is the volume of the diluted solution of the drug, ml, and V_2 is the volume of the aliquote part of this solution taken for the determination, ml.

The State Pharmacopoeia requires that the content of $C_6H_6O_2$ be at least 99.5%.

4. Compare the result obtained with the official requirement and make the corresponding conclusion.

Chapter 20. Aromatic Acids and Their Derivatives

(Independent Work. Problem Solving Research Method)

Study the following topics independently.

1. General characteristic of the aromatic acids (preliminarily repeat the topic "Aromatic Acids" in the course of organic chemistry).

2. Benzoic acid.

3. Sodium benzoate.

4. Salicylic acid.

5. Sodium salicylate.

6. Phenylsalicylate. Essence of Nentsky's principle.

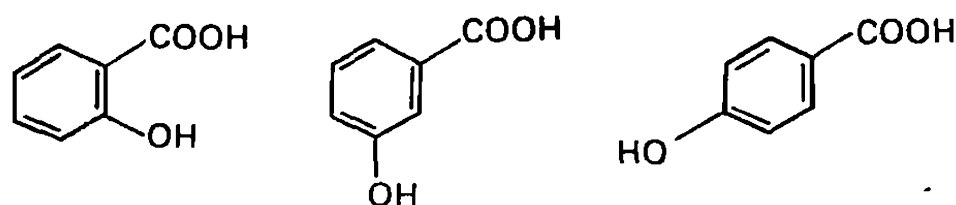
7. Acetylsalicylic acid.

If an acid is a carboxylic one, what functional group characterizes the compound? Write this down.

If an acid belongs to the aromatic series, what nucleus does it contain? Write this down.

Compile the formula of the simplest representative of the aromatic carboxylic acids (the simplest representative is benzoic acid).

The introduction of the functional group OH into various positions in a molecule of benzoic acid determines a variety of aromatic acids:



Phenol acids (hydroxybenzoic acids)

By analogy with the phenol acids, introduce an amino group into the benzoic acid molecule instead of the hydroxyl group. Write these compounds and name them.

The aromatic acids are crystalline substances, generally slightly soluble in water and well soluble in polar organic solvents (alcohol,

chloroform, benzene). Their dissociation constants are somewhat higher than those of the aliphatic acids.

The aromatic acids have all the properties characteristic of the carboxylic acids of the aromatic series. They form salts, anhydrides, halogen anhydrides, amides, esters, etc. Give examples of the above compounds.

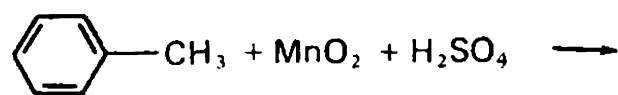
In medicine, the aromatic acids are employed as weak antiseptics, and their salts as carriers of specific cations.

Benzoic Acid (*Acidum benzoicum*)

Write the Latin name and formula in your notebook.

Benzoic acid was first discovered in benzoic gum. It is encountered in the free state in some resins and balsams, for example in Peru and Tolu balsam, and in cranberries.

Benzoic acid is contained in large amounts in the form of an ester in benzoic resin, from which it was produced by sublimation. Benzoic acid is produced for medicinal purposes from toluene by oxidizing it with manganese dioxide in an acidic medium:



Complete the equation of the reaction.

Use samples of the preparation to study its physical properties: appearance, odour, solubility.

Put 0.1 g of benzoic acid into each of four test tubes. Add 2-3 ml of cold water to the first tube and shake it. Write what you observe in your notebook. Next heat the contents of the tube up to boiling. Comment on your observations.

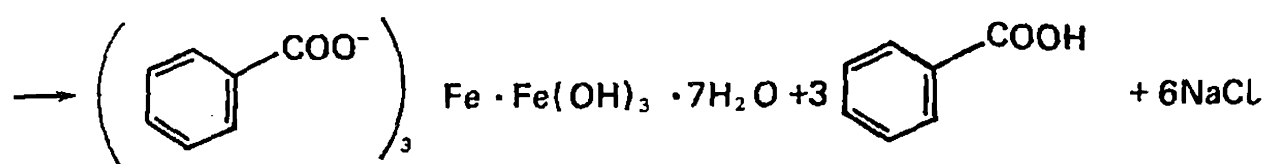
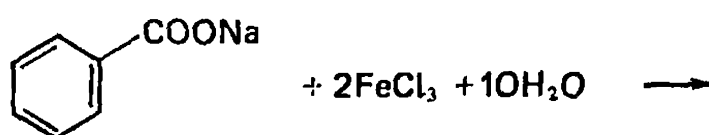
Add 1 ml of alcohol to the second tube, 1 ml of chloroform to the third, and 1 ml of ether to the fourth one. See how benzoic acid dissolves in various solvents.

A typical property of benzoic acid is its ability to sublime when heated. Check this experimentally.

How can benzoic acid be identified?

Carry out a reaction with a solution of iron(III) chloride after first neutralizing the benzoic acid with an alkali (using an indicator) because the precipitate of the complex salt dissolves in an acidic medium, while iron hydroxide precipitates with an excess of the alkali (see the State Pharmacopoeia). Write the equations of the

reactions in your notebook:



How can benzoic acid be determined quantitatively?

Name the method, outline the procedure of the quantitative determination, and explain why the sample has to be dissolved in alcohol. Write the equation of the chemical reaction.

Benzoic acid is employed as a weak antiseptic; it also acts as an expectorant.

What are the requirements to the storage of the drug?

Sodium Benzoate (*Natrii benzoas*)

Write the Latin name, chemical and structural formula of sodium benzoate. How can sodium benzoate be produced?

Characterize the physical properties of sodium benzoate (State Pharmacopoeia). Indicate its solubility in water. Compare it with the solubility of benzoic acid.

How can sodium benzoate be identified?

Will a reaction with an iron(III) chloride solution be positive?

Add hydrochloric acid to a sodium benzoate solution. What do you observe? Write the equations of the chemical reactions.

A reaction with a 5% copper sulphate solution is a specific (but not official) one; a turquoise precipitate forms.

How can sodium benzoate be determined quantitatively? Name the method. Write the equation of the chemical reaction.

How should sodium benzoate be stored?

What is sodium benzoate used for in medicine? Why does sodium benzoate have a milder action on an organism than benzoic acid?

Chapter 21. Phenol Acids and Their Derivatives

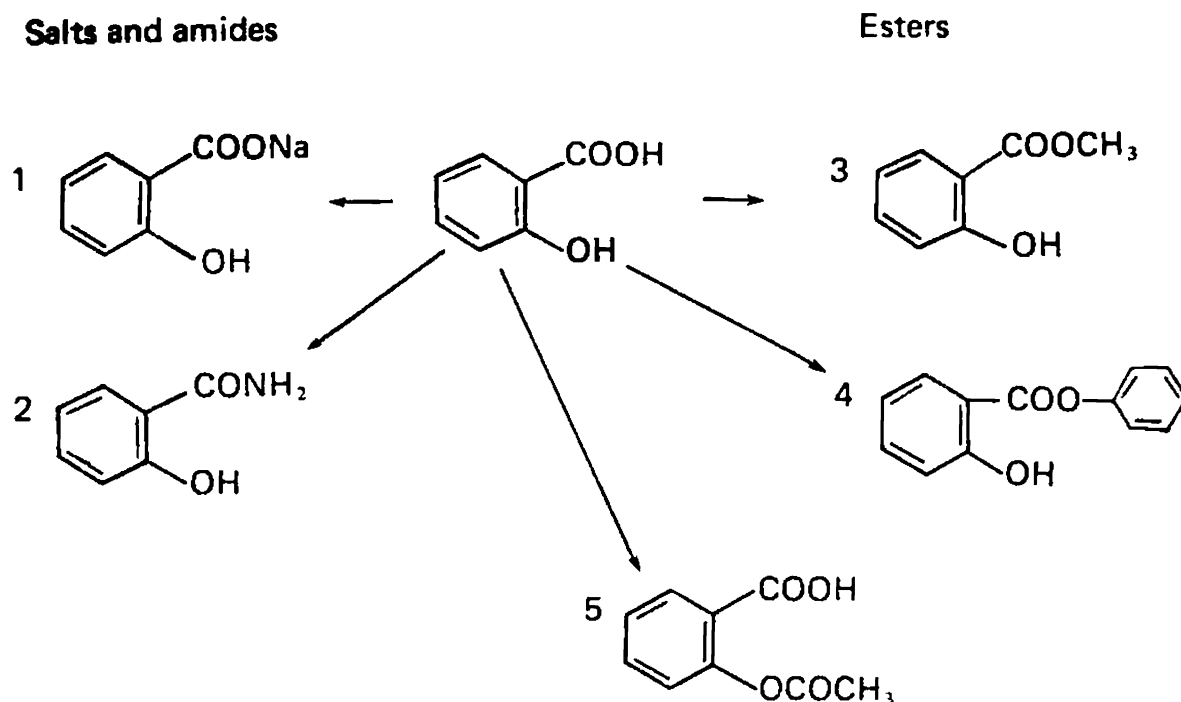
(Independent Work. Problem Solving Research Method)

Which derivatives of the aromatic acids are called phenol acids? Write three possible isomers of the phenol acids and name them.

Ortho-hydroxybenzoic or salicylic acid is employed in medicine because it is the only one of the three isomers that exhibits physiological activity.

At present, derivatives of salicylic acid are widely used in medicine, namely:

1. Salts formed via the carboxyl group (sodium salicylate).
2. An amide of salicylic acid (salicylamide).
3. Esters formed via the carboxyl group (methyl and phenyl).
4. Esters formed at the expense of the phenol hydroxyl (acetylsalicylic acid, or aspirin):



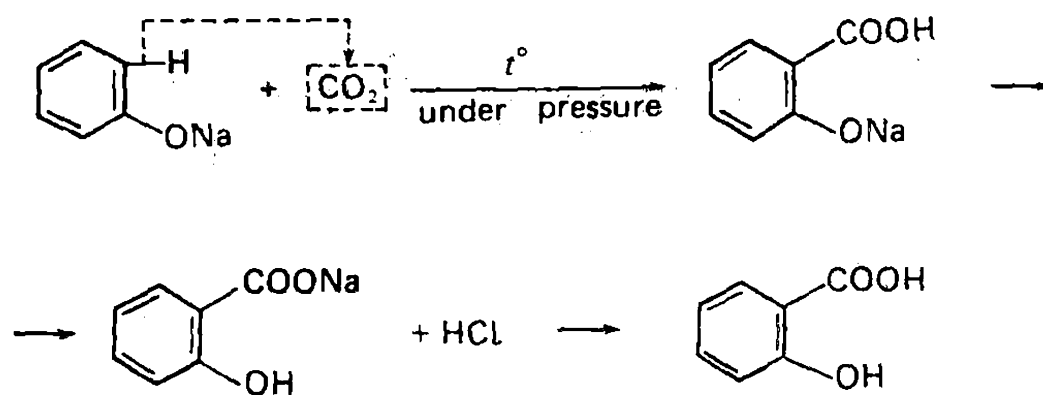
All these derivatives have a similar action but it also differs somewhat. For example, sodium salicylate and salicylamide are taken orally to treat rheumatism; alkyl esters (methylsalicylate) are absorbed better through the skin and are employed externally in rheumatism. Acyl esters (acetylsalicylic acid) have an antipyretic and analgesic action, while phenyl ester (phenylsalicylate) is an antiseptic.

Salicylic Acid (*Acidum salicylicum*)

Write the Latin and chemical name of salicylic acid and its formula.

Salicylic acid is found in nature both in the free state (flowers of the wild camomile and a species of the willow) and in the bound state in many essential oils (clove, tuberose, etc.).

Salicylic acid is prepared from sodium phenolate as follows:



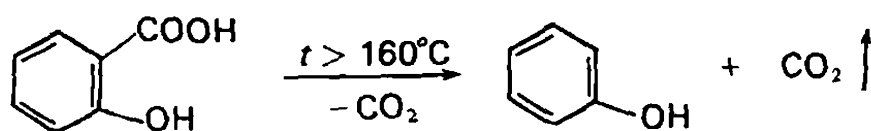
Here intramolecular regrouping occurs. Explain it and write it down in your notebook.

Use samples of the preparation to study the physical properties of salicylic acid. Describe the appearance of the crystals.

Put 0.1 g of salicylic acid into each of three test tubes. Add 2 ml of water to the first tube, 1 ml of alcohol to the second, and 1 ml of ether to the third one. See how salicylic acid dissolves in various solvents.

When carefully heated, salicylic acid sublimes. Verify this experimentally.

When heated to above 160 °C, salicylic acid transforms into phenol. Verify this experimentally. How can the phenol be detected?

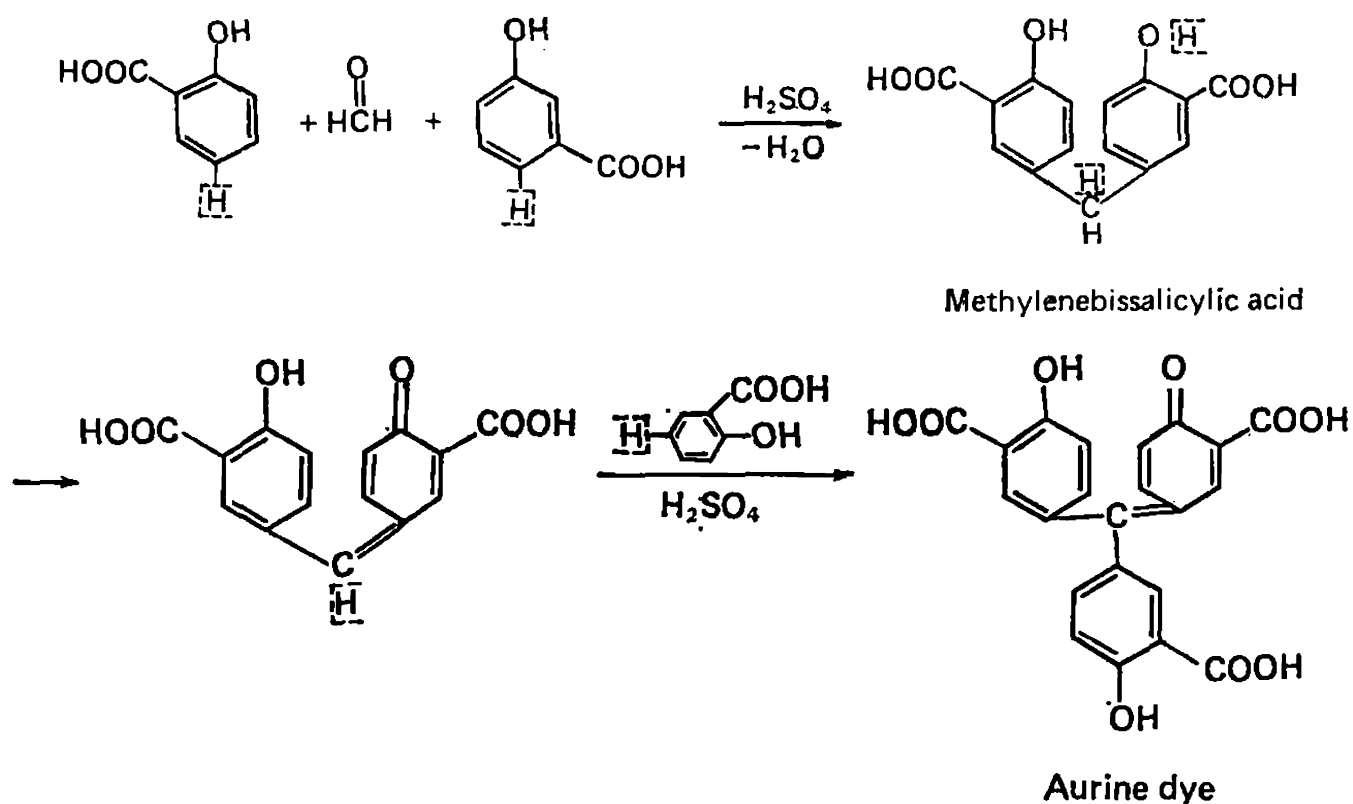


What happens to the salicylic acid? What is this process called?

Perform identification reactions (State Pharmacopoeia). Conduct a reaction with an iron(III) chloride solution. What colour appears? How can it be explained?

Of interest is the non-pharmacopoeial reaction of salicylic acid with Marchi's reagent (a solution of formaldehyde in concentrated

sulphuric acid), as a result of which a red colour appears:



How is salicylic acid determined quantitatively? Name the method used, outline the procedure to be used for the quantitative determination, explain why the sample is to be dissolved in alcohol, and write the equation of the chemical reaction.

The drug is not taken orally because it has an irritating effect. Salicylic acid is employed externally as an antiseptic and fungicide. Write in your notebook the conditions of storage of salicylic acid and explain them.

Sodium Salicylate (*Natrii salicylas*)

Write the Latin name, structural and chemical formula of sodium salicylate (State Pharmacopoeia).

What type of compound does this preparation belong to?

How is sodium salicylate produced?

Characterize the physical properties of sodium salicylate and its solubility in water. Compare its solubility with that of salicylic acid (State Pharmacopoeia).

How is sodium salicylate identified? Write the equations of the chemical reactions.

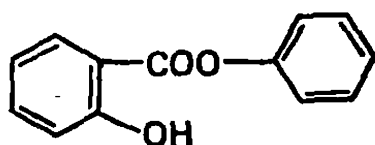
The reaction with a 5% copper sulphate solution producing an intensive green colour is a characteristic (but not official) one.

How can sodium salicylate be determined quantitatively? Name the method. Why must titration be performed in the presence of ether? Write the equation of the chemical reaction.

What are the requirements to the storage of sodium salicylate? It is employed to treat rheumatism.

Phenyl Salicylate (*Phenylii salicylas*)

Write the Latin name and structural formula of phenyl salicylate into your notebook:

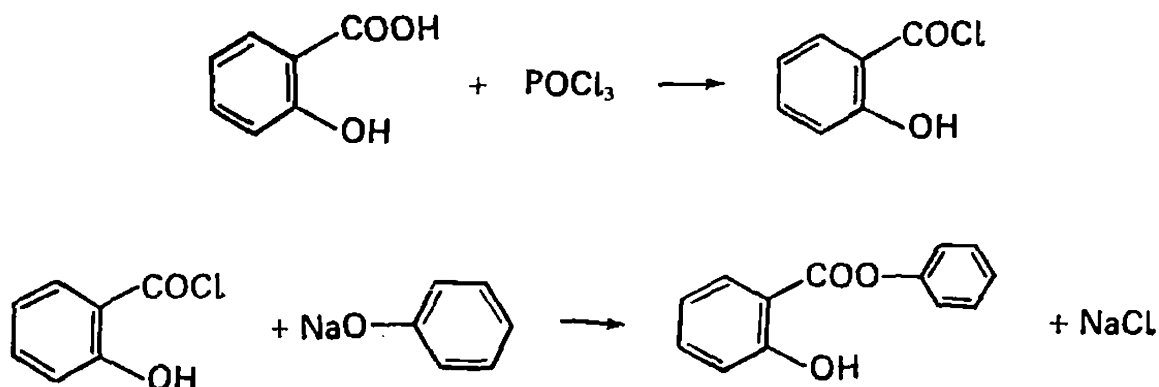


Underline the functional group showing that phenyl salicylate (salol) is an ester.

Phenyl salicylate was first prepared by M. Nentsky (1886). His aim was to obtain a drug such that would retain the antiseptic properties of phenol but would not have the irritating action of salicylic acid. For this purpose, he blocked the carboxyl group in salicylic acid and obtained its ester with phenol. Phenyl salicylate does not change in the stomach, while in the alkaline medium of the intestines it hydrolyzes to form the sodium salts of salicylic acid and phenol, which are just what exhibit a healing effect. Since hydrolysis proceeds slowly, the products of hydrolysis of phenyl salicylate form gradually and do not accumulate in large amounts. This ensures the more prolonged action of the drug. This principle of introducing substances with an irritating effect into an organism in the form of their esters went down in the literature as Nentsky's "salol principle" and was later used for the synthesis of many drugs.

Phenyl salicylate is often employed to coat pills if the latter are to pass unchanged through the stomach and liberate the drugs they contain in the intestines.

Phenyl salicylate is prepared synthetically. Write down the scheme of synthesis and name the intermediates:



Use specimens of the preparation to study its physical properties—its appearance and odour. Test its solubility in water, alcohol, ether, and chloroform. Write down your conclusions in your notebook. Check whether phenyl salicylate dissolves in sodium hydroxide. Explain the result from a chemical viewpoint.

Phenyl salicylate forms eutectic mixtures with camphor, menthol, and thymol. The melting point of phenyl salicylate is 42-43 °C.

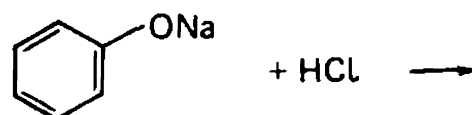
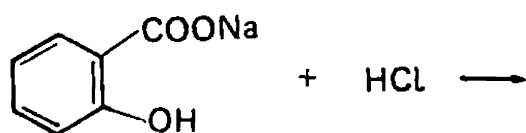
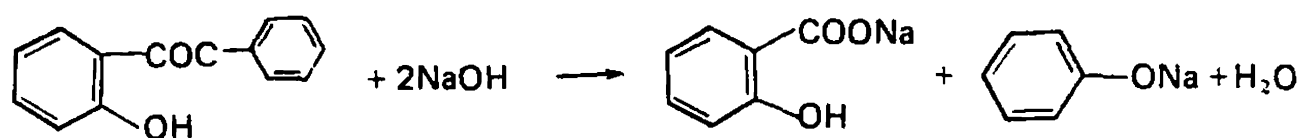
Identify phenyl salicylate:

1. React an alcohol solution of phenyl salicylate with an iron(III) chloride solution. What colour appears? Why is the reaction carried out in an alcohol medium?

2. Perform a reaction with concentrated sulphuric acid with the following addition of formalin. What colour is observed? Explain the chemism of the reaction. What is the role of the sulphuric acid? Why is a smell of phenol felt? With what does the formalin react to produce a pink colour (an aurine dye)? Write the equations of the chemical reactions.

3. Dissolve about 0.1 g of the preparation in 5 ml of sodium hydroxide, boil the solution for three minutes, cool it, and add hydrochloric acid. A white precipitate appears and a smell of phenol is felt.

Complete the equations of the reactions:



Determine phenyl salicylate quantitatively (State Pharmacopoeia).

Put an accurately weighed sample of the preparation into a flask, and add an exact volume of a titrated sodium hydroxide solution. Insert a reflux condenser and heat the mixture in a boiling water bath. Explain the process that occurs. Next titrate the excess sodium hydroxide with hydrochloric acid until the indicator (bromocresol purple) gives a stable yellow colour. Write the equations of the reactions.

Indicate the method used to perform the quantitative determination.

What is the drug used for and why?

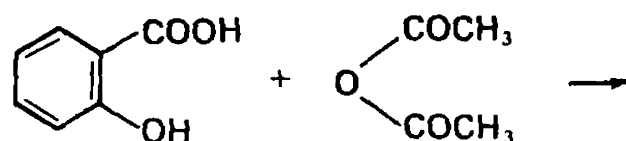
What requirements must the storage of phenyl salicylate meet and why?

Acetylsalicylic Acid (*Acidum acetylsalicylicum*)

Write the Latin name of acetylsalicylic acid (State Pharmacopoeia) and its structural formula.

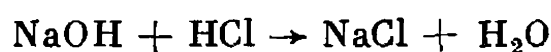
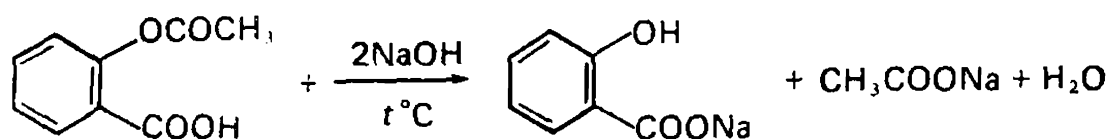
What is acetylsalicylic acid from the chemical viewpoint? Propose possible ways of producing it.

Write the equation of the chemical reaction of salicylic acid with acetic anhydride (the reaction mixture is heated to 50-60 °C):



Use specimens of the preparation to study its physical properties, namely, the appearance of the crystals, odour, and taste. Test the solubility of acetylsalicylic acid in water, alcohol, chloroform, ether, and in alkali metal hydroxides and carbonates. Write down your conclusions and observations.

Acetylsalicylic acid can be determined quantitatively by neutralization after hydrolysis (with the following titration of the excess sodium hydroxide with an acid using a methyl orange indicator):



A gramme-equivalent in the given case equals $M/2$.

Acetylsalicylic acid does not change in the stomach, while it partly hydrolyzes in the intestines. Name the hydrolysis products.

Acetylsalicylic acid is partly absorbed unchanged. It is administered as an antipyretic and analgesic drug. With some substances of a basic nature (hexamethylenetetramine, carbonates), acetylsalicylic acid produces mixtures that readily become damp. This must be taken into account when writing prescriptions and preparing drugs with such substances.

What requirements must storage of the drug meet?

REVIEW QUESTIONS

1. What chemical properties do aromatic acids have and what are they due to?
2. How can the ability of aromatic acids to form salts, anhydrides, halogen anhydrides, amides, and esters be explained?
3. What chemical properties of benzoic acid are used in the reaction of formation of various precipitates with salts of the heavy metals?
4. What method is used for the quantitative determination of benzoic acid?
5. Why must the titration of a sample of benzoic acid be performed in an alcohol medium?
6. Explain why sodium benzoate acts on an organism more mildly than benzoic acid.
7. Why is sodium benzoate determined quantitatively in the presence of ether?
8. What happens to salicylic acid when heated to 160 °C?
9. Which functional group of salicylic acid explains its reaction with Mar-chi's reagent and iron(III) chloride?
10. Why does the blue-violet colour formed when salicylic acid is reacted with an iron(III) chloride solution disappear when a mineral acid is added and fail to disappear when an organic acid is added?
11. What reaction can be used to distinguish sodium salicylate from sodium benzoate?
12. Why is the quantitative determination of sodium salicylate by neutral-ization performed in the presence of ether?
13. What is the essence of Nentsky's principle?
14. Why is phenyl salicylate employed for coating pills? In what cases?
15. When the content of acetylsalicylic acid is determined relative to the carboxyl group by neutralization, titration is conducted in an alcohol medi-um. Why?

PRACTICAL LESSON

Analysis of Acetylsalicylic Acid

1. Perform an identification reaction.
Dissolve about 0.1 g of the drug in 5 ml of a potassium hydroxide solution, boil it for three minutes, and after cooling acidify the solution with sulphuric acid. A white crystalline precipitate forms and a smell of acetic acid is felt. Write the equations of the chemical reactions.
2. Conduct a quantitative determination (by neutralization).
Put 0.05 g of the drug into a conical flask for titration and dissolve in 3 ml of alcohol. Next add 5 ml of water, three drops of a phenolphthalein indicator and titrate with a 0.1 *N* sodium hydroxide solution until a pink colour appears. Write the equation of the chemical reaction.
3. Calculate the content of the acetylsalicylic acid in per cent in the drug by formula (1.1):

$$X = \frac{VKT}{a} \times 100 = \frac{VK \times 0.018}{0.05} \times 100$$

where *V* is the volume of the 0.1 *N* sodium hydroxide solution, ml, *T* = 0.018 g/ml, and *a* is the mass of the sample taken for the determination, g.

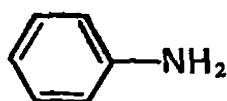
The State Pharmacopoeia requires that the content of $C_9H_8O_4$ be at least 99.5%.

4. Conclude on the correspondence of the drug to the official requirements and on the possibility of its administration.

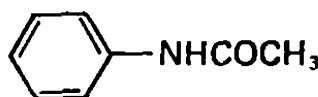
Chapter 22. Aminoderivatives of the Aromatic Series

The simplest amine of the aromatic series is aniline (I), which is toxic and is not employed in medicine. Its acetylated derivative acetanilide (II) is less toxic and was used for a certain period in medicine under the name of antifebrin as an antipyretic. But the prolonged oral administration of this drug quite often resulted in poisoning because upon saponification of the acetyl group, toxic aniline accumulated in an organism.

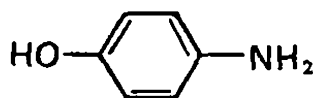
When studying the products of the transformation of aniline and acetanilide in an organism, their oxidation product *p*-aminophenol (III) was found to be less toxic, but unlike acetanilide it has no antipyretic effect and like aniline destroys erythrocytes:



I

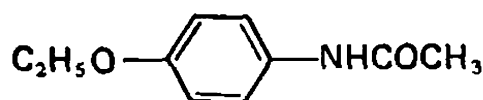


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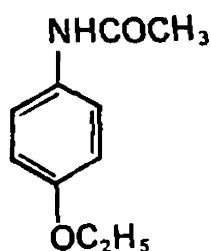
III

Further studies led to the conclusion that to eliminate these shortcomings it is necessary to block the hydroxyl and amino groups in the aromatic ring. This resulted in the creation of a drug called phenacetin:



Phenacetin has a weaker haemolytic action on the erythrocytes and at the same time has an antipyretic effect. The presence of the ethoxy group imparts a light narcotic action to phenacetin, which increases the significance of this drug because it can also be employed as an analgesic.

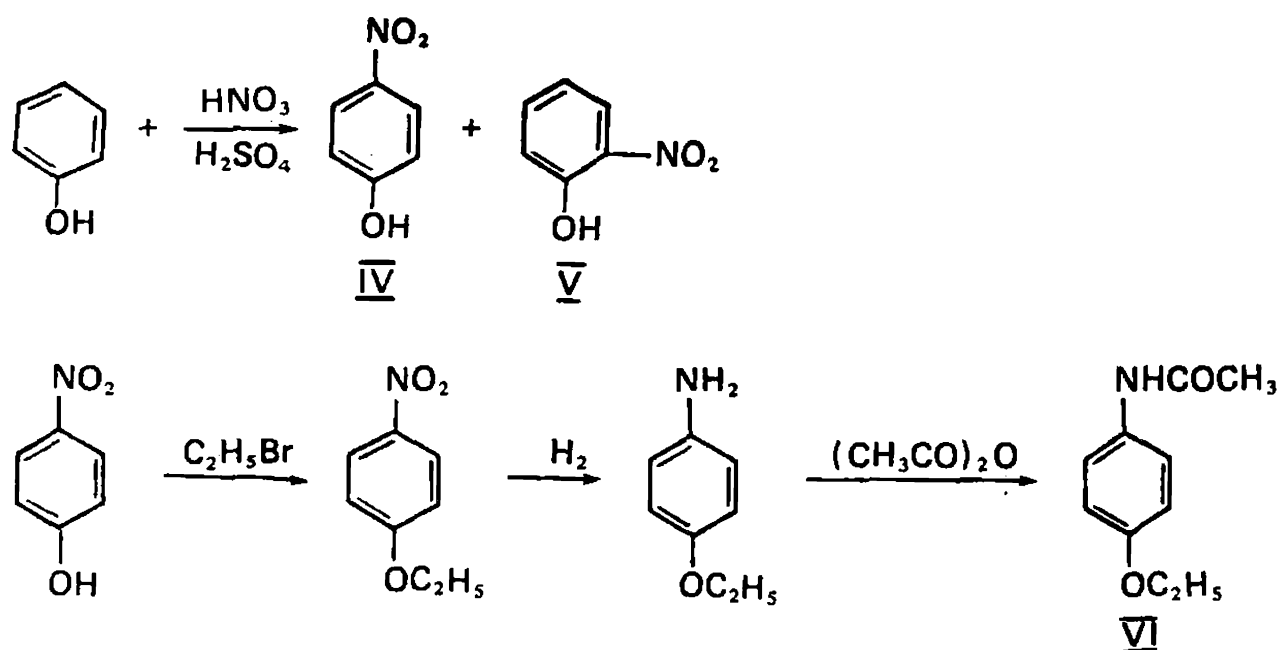
Phenacetin is a pharmacopoeial drug.

Phenacetin (*Phenacetinum*)*1-Ethoxy-4-acetaminobenzene* $C_{10}H_{13}NO_2$

M.m. 179.22

Among the numerous methods of producing phenacetin, the most widespread one is that of producing it from *para*-nitrophenol (IV)—a by-product in the production of dyes.

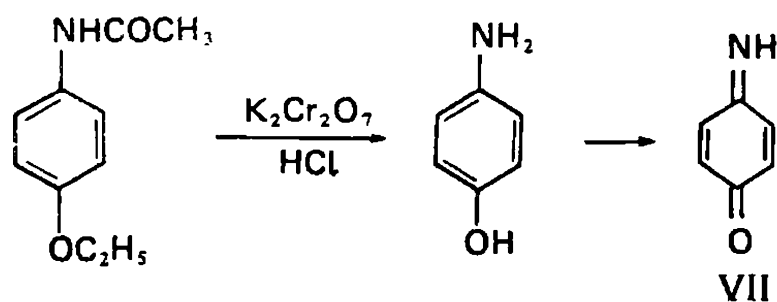
The initial substance is phenol, which is nitrated by an appropriate mixture to produce two isomers: *ortho*- and *para*-nitrophenols (V, IV). To separate them, the mixture is distilled with steam (*ortho*-nitrophenol evaporates with steam). Next the *para*-nitrophenol is ethylated and reduced. The reduced product is acetylated to form phenacetin (VI):



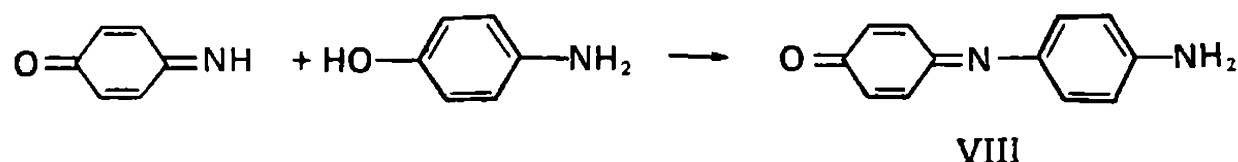
Phenacetin is a white finely crystalline odourless powder with a slightly bitter taste. It dissolves very sparingly in water, sparingly in boiling water, it is soluble in 95% alcohol, and poorly soluble in ether and chloroform.

Phenacetin gives a colour reaction with a potassium dichromate solution in an acidic medium, which is the official reaction for iden-

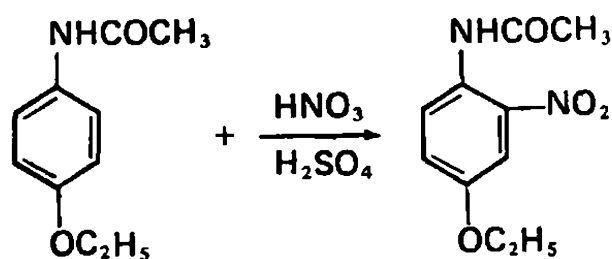
tifying the drug:



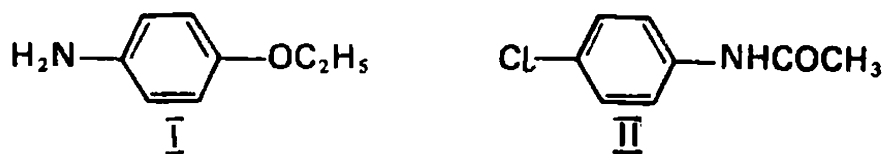
The resulting quinone imine (VII) can enter into a reaction with the unreacted *para*-aminophenol to form an indophenol dye (VIII) having a blue-violet colour:



When phenacetin is reacted with dilute nitric acid, the solution turns yellow, and then a yellow precipitate of 3-nitro-4-acetaminophenetol forms (State Pharmacopoeia):



The State Pharmacopoeia requires that the drug contain no admixtures of acetanilide, *para*-phenetidine (I), and *para*-chloroacetanilide (II) that may form in the production of phenacetin:

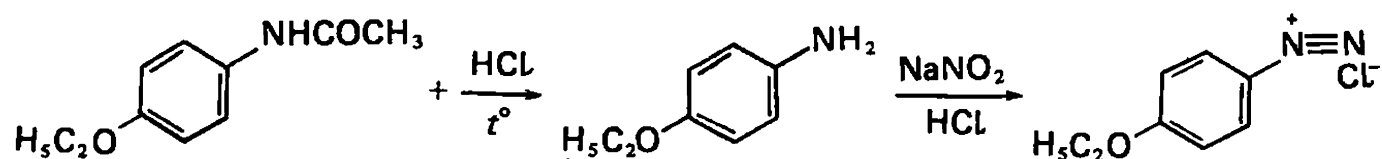


In prolonged or improper storage of the drug, acetic acid may evolve, therefore the State Pharmacopoeia establishes the maximum tolerated acidity in the drug.

Phenacetin is dispensed in powders and tablets—*Tabulettæ Phenacetini* 0.25 g.

The State Pharmacopoeia recommends determining the content of phenacetin in tablets by nitritometry. An exactly weighed sample of tablets is ground into a powder, a hydrochloric acid solution is added, and the mixture is heated for 30 minutes. The *para*-phenetidine formed in the hydrolysis process is titrated with sodium nitrite in

the presence of a mixed indicator consisting of tropeolin-00 and methyl blue. At the equivalence point, the red-violet colour of the solution turns light blue-green:

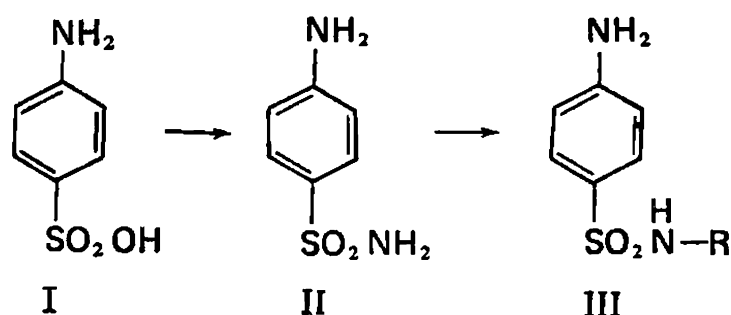


Phenacetin is taken orally as an antipyretic and analgesic. It should be stored in well closed containers. It is listed in Group B.

Chapter 23. Sulphanilic Acid Amides

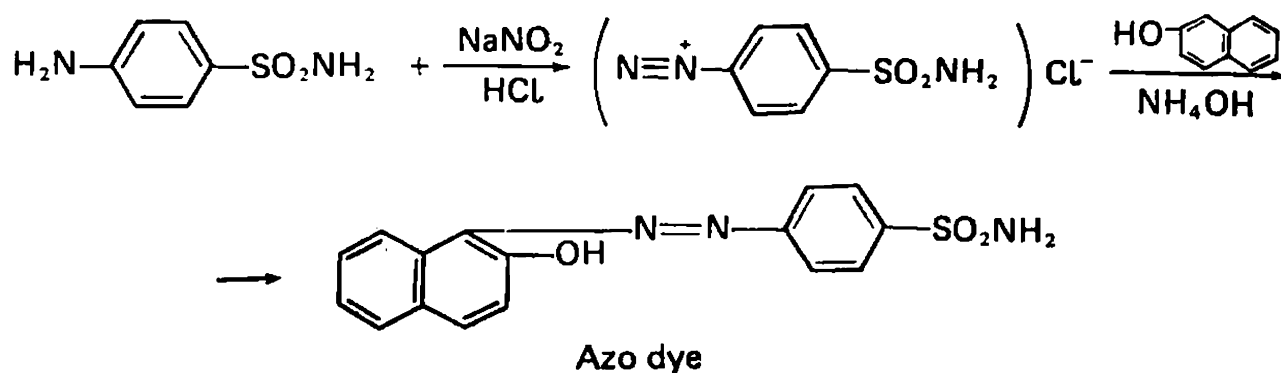
(Sulphanilamide Drugs)

Sulphanilic acid (I) is not a drug, but its amide (II) is one (streptocid or sulphanilamide) and is a source for the preparation of a large number of drugs combined as regards their chemical structure and physiological action into a single large group of sulphanilamide drugs of the general formula (III):

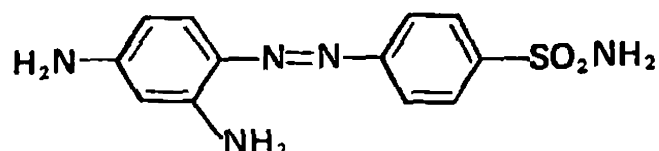


where R stands for a large variety of substituents.

The sulphanilamide drugs were discovered by chance. This was associated with the textile industry, when the French chemist J. Helmont (1909) synthesized *para*-aminobenzosulphamide as a source for producing a dye:



After it became known that the dyes exhibit an antimicrobial activity, the German scientist G. Domagk (1932) obtained an azo dye, which he called prontosil, that exhibited a high therapeutical activity in severe streptococci infections:



Prontosil

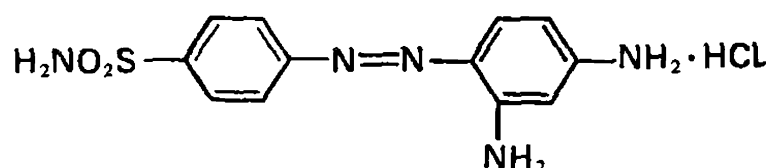
This discovery was the beginning of a new stage in the development of chemotherapy. The fundamental task of chemotherapy is the synthesis of drugs for combatting infectious diseases. Substances acting selectively on pathogenic microorganisms and virtually not acting in the same concentrations on macroorganisms are called **chemotherapeutic drugs**.

The fundamentals of chemotherapy were first formulated by the Russian scientist D. Romanovsky (1891).

The high activity of sulphanilamide drugs in the treatment of diseases previously resulting in a high death rate (lobar pneumonia, meningitis, gaseous gangrene, erysipelas, etc.) aroused great interest in these compounds among scientists in many countries of the world including chemists, biologists, microbiologists, and clinicians.

The creation of sulphanilamides in the USSR relates to 1935-36. These years saw the appearance of the first works in the synthesis and studying of the therapeutic properties of sulphanilamides carried out in the USSR by the well known organic chemist O. Magidson.

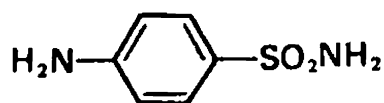
The first sulphanilamide drug created by the Soviet chemists (Magidson and M. Rubtsov) was red streptocid, close in its chemical structure to the foreign-made prontosil and sulphachrysoidine:



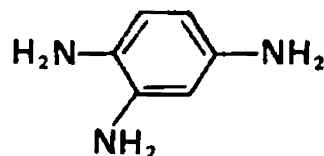
Red streptocid

It was soon found that prontosil and, consequently, red streptocid closely related to it, decompose in an animal's organism with the formation of two products, namely, sulphanilamide (I) (a highly active therapeutic drug), and 1,2,4-triaminobenzene (II) (a toxic,

physiologically inactive product):



I

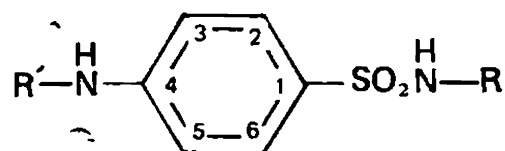


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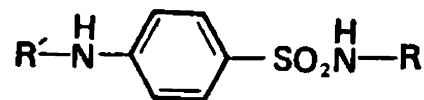
This circumstance made chemists refute compounds of the type of prontosil and red streptocid and concentrate all their attention on sulphanilamide, which exhibits a high therapeutic activity. From this time, *para*-aminobenzenesulphamide (I) was acknowledged throughout the world.

In the USSR it was introduced into medical practice in 1936 under the name "white streptocid" in contrast to the previously created "red streptocid".

Hence, white streptocid (sulphanilamide), which now bears the official name of streptocid, is the parent of the entire group of sulphanilamide drugs. By replacing the hydrogen in the sulphamide group (position 1) and in the aromatic amino group (position 4) with various radicals, a multitude of sulphanilamide drugs with a varying degree of therapeutic activity were produced from streptocid:



The development of sulphanilamide drugs both in the USSR and in other countries was very rapid, especially during the first decade after their discovery. By this time, medicine had at its disposal sulphanilamide drugs of the general structural formula



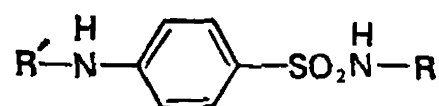
The following drugs were produced when R and R' were hydrogen or the relevant functional group:

Streptocid (sulfachrysoidine)	R = H	R' = H
Soluble streptocid	R = H	R' = $-\text{H}_2\text{CSO}_3\text{Na}$
Sulphacyl (sulphacetamide)	R = $-\text{COCH}_3$	R' = H

Norsulphazol (sulphathiazole)	$R = \text{—} \begin{array}{c} \text{N} \\ \diagup \quad \diagdown \\ \text{C} \quad \text{S} \end{array}$	$R' = \text{H}$
Sulgin (sulphaguanidine)	$R = \text{—} \text{C} \begin{array}{l} \diagup \text{NH} \\ \diagdown \text{NH}_2 \end{array}$	$R' = \text{H}$
Sulphadimezine (sulphadimedine, sulphamethazine)	$R = \text{—} \begin{array}{c} \text{CH}_3 \\ \diagup \quad \diagdown \\ \text{N} \quad \text{C} \\ \diagdown \quad \diagup \\ \text{N} \quad \text{C} \\ \diagup \quad \diagdown \\ \text{CH}_3 \end{array}$	$R' = \text{H}$
Ethazole (sulphaethidole)	$R = \text{—} \begin{array}{c} \text{N} \\ \diagup \quad \diagdown \\ \text{C} \quad \text{S} \end{array}$	$R' = \text{H}$
Urosulphan (sulphacarbamide, sulphaurea)	$R = \text{—} \text{C} \begin{array}{l} \diagup \text{O} \\ \diagdown \text{NH}_2 \end{array}$	$R' = \text{H}$
Phthalazole (phthalylsulphathiazole)	$R = \text{—} \begin{array}{c} \text{N} \\ \diagup \quad \diagdown \\ \text{C} \quad \text{S} \end{array}$	$R' = \text{—} \text{C} \begin{array}{c} \text{O} \\ \parallel \\ \text{C}_6\text{H}_4 \\ \text{COOH} \end{array}$

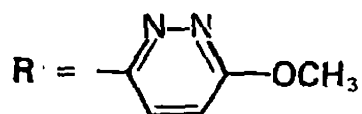
But by 1944-1945, the first antibiotics (penicillin, streptomycin, gramicidin, etc.) appeared in chemotherapy, and the interest in sulphanilamide drugs dropped somewhat. This was facilitated by the circumstance that the sulphanilamides act for only a short time, and although they are absorbed well, are rapidly excreted from the organism, which makes high doses necessary. Moreover, some micro-organisms rapidly acquire immunity to these drugs, while still larger doses increase their toxicity.

In this connection, work was commenced for creating sulphanilamides with prolonged action that would retain the structure of para-aminobenzenesulphamide, but would have different radicals. The result was the appearance of drugs with a prolonged action and of the general structural formula:



The following drugs were obtained, where R and R' were hydrogen or the relevant functional group:

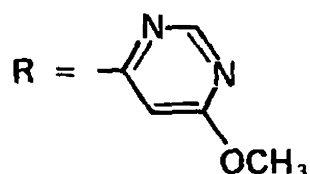
Sulphapyridazine



R' = H

3-Methoxypyridazine

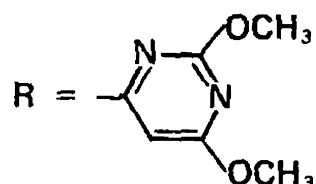
Sulphamonomethoxine



R' = H

6-Methoxypyrimidine

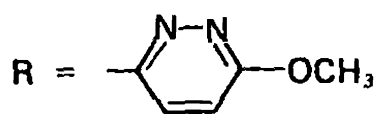
Sulphadimethoxine



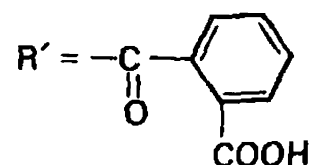
R' = H

2,4-Dimethoxypyrimidine

Phthazine



6-Methoxypyridazine

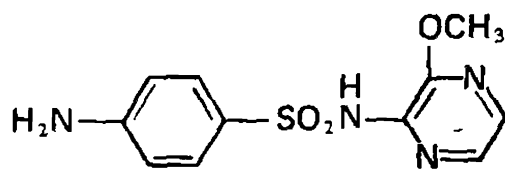


Unlike the sulphanilamides with brief action, these drugs create a high concentration in the blood and remain for a long time in the organism. This makes it possible to lower their doses, which, in turn, substantially reduces the possibility of undesirable side effects.

Generally sulphanilamides with brief action are prescribed in doses of 6.0 g a day (to be taken every four hours).

Drugs with a prolonged action are prescribed in a dose of 1.0 g the first day, and then 0.5 g a day.

One of the latest and more improved sulphanilamides of this group is the drug sulphalene with a superprolonged action:



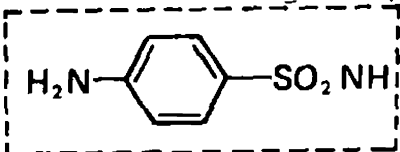
in whose molecule R is 6-methoxypyrazine.

The half-life of this drug in the blood averages 65 hours.

When treating chronic diseases, sulphalene is prescribed in a daily dose of 1.0 g during 7-10 days, while when treating acute and rapidly proceeding infections, in a daily dose of 0.2 g.

To date a large number of sulphanilamides with prolonged action have been synthesized having the most diverse radicals in a molecule.

Since all the sulphanilamides are based on the same structure—the

sulphanilamide residue , their synthesis is

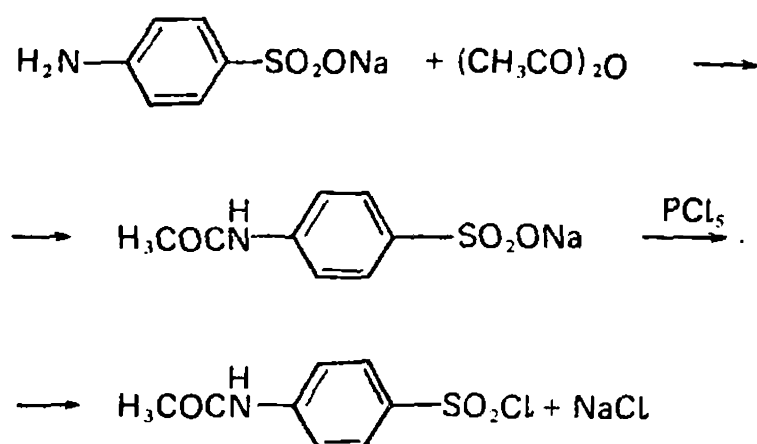
approximately the same:

I. The preparation of the chloranhydride of acylsulphanilic acid.

II. The preparation of the corresponding amino derivative (R—NH₂).

III. Condensation of the chloranhydride of sulphanilic acid with the amino derivative (R—NH₂).

The first stage is common for all the sulphanilamides. Since sulphanilic acid cannot be directly transformed into its chloranhydride, it is first acetylated with acetic anhydride, and then the chloranhydride is obtained by a reaction with phosphorus pentachloride. Sodium sulphanilate is taken for acetylation:



The second stage of synthesis is individual for each drug and depends on the nature of R.

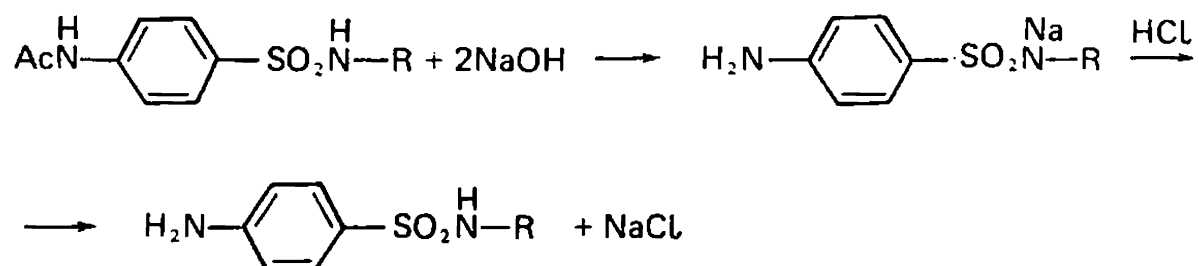
In the third stage, the chloranhydride of acylsulphanilic acid prepared in stage I is condensed with the relevant amine:



The reaction should be conducted in a weakly alkaline medium to neutralize the evolving hydrochloric acid that would otherwise enter into a reaction with the amine to form hydrochlorides, when the

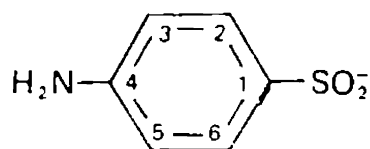
reaction of condensation of the amine with the chloranhydride of acylsulphanilic acid does not proceed.

The acyl group is then saponified because acylated compounds have no therapeutic action. Saponification of the acyl group is performed with an alkali (NaOH), hence the product of saponification is obtained in the form of a soluble sodium salt. It is treated with an acid and then purified. As a result, the corresponding sulphanilamide forms:



Simultaneously with the synthesis of sulphanilamide drugs, the relation between the chemical structure of the sulphanilamides and their physiological action was investigated. The main laws of this relation consist in the following:

1. The physiological activity of the sulphanilamides is due to the presence of the sulphanil radical in the molecule:



2. The transition of the amino group from position 4 to other positions of the aromatic ring leads to the complete loss of physiological activity.

3. Any sulphanilamide derivative with a substituted amino group in position 4 can be physiologically active only if a free amino group can form again in an organism.

4. The introduction of additional substituents into the aromatic ring either eliminates or reduces the physiological activity.

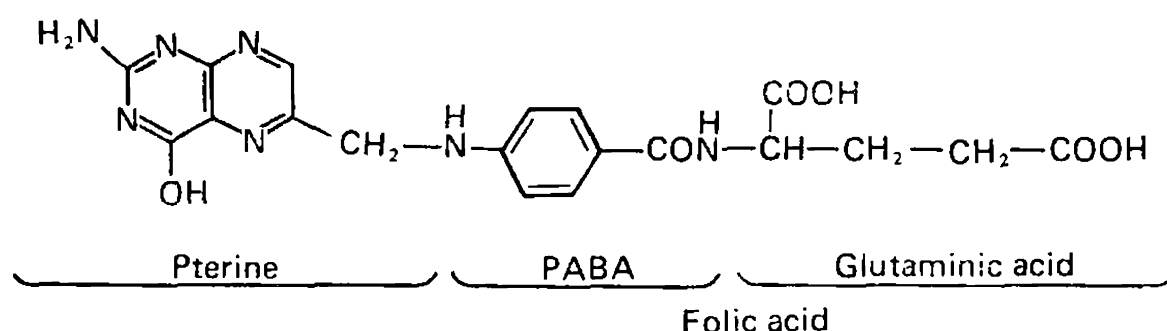
5. When various radicals are introduced into the sulphonamide group of the molecule, the physiological activity can either grow or diminish depending on the nature of the radical.

6. The presence of methoxy groups in a molecule is of substantial importance for the prolonged action of the drug (almost all the drugs with a prolonged action, unlike those with a brief action, have a methoxy group OCH_3 in the heterocyclic nucleus—R).

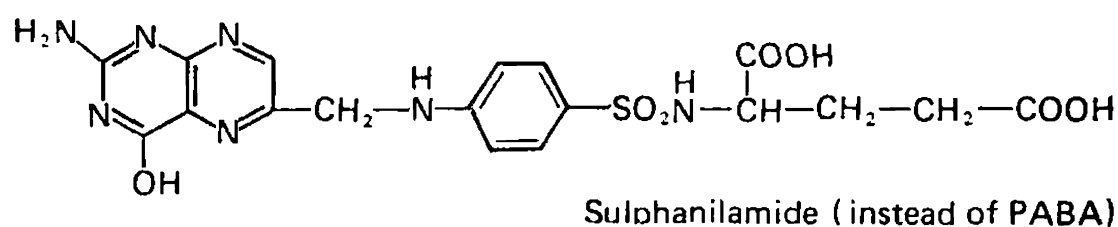
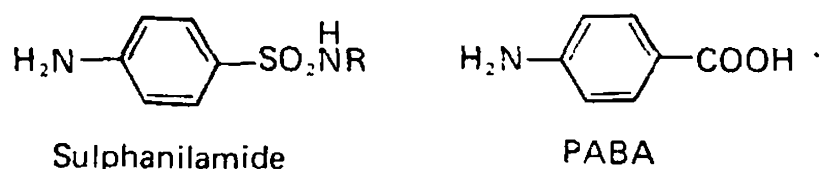
It is presumed that the methoxy group determines the higher binding of the sulphanilamide with the plasma proteins, which is exactly what underlies the prolonged action of a drug.

The mechanism of the antimicrobial action of the sulphanilamides is associated with their competitive antagonism with *para*-amino-benzoic acid (PABA).

Folic acid is needed for the normal vital activities and growth of many microorganisms. It is synthesized in a microbe cell from PABA, glutaminic acid, and pterine:



Since the sulphanilamides have a chemical structure similar to PABA, they prevent its inclusion into the folic acid molecule, occupying its place:



The formed compound deprived of PABA can no longer be used by the microbe cell as a nutritive enzyme, and the microorganisms stop growing.

Thus, unlike bactericides or antiseptics, which kill microorganisms owing to the denaturation of their proteins, sulphanilamides have a bacteriostatic action, which is associated with disturbance of the biosynthesis of folic acid—a vitally required nutrient complex for microbes, and they stop reproducing.

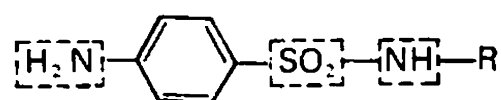
The theory underlying the mechanism of action of the sulphanilamide drugs resulted in the discovery of new antagonists for other classes of compounds such as vitamins.

All the sulphanilamide drugs are crystalline odourless powders of a white or slightly yellowish colour. Their acidic forms dissolve poorly in water, but dissolve well in some organic solvents such as alcohol and acetone. Each drug has a specific melting point. The

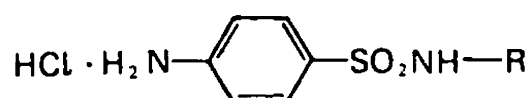
sodium salts of the sulphanilamides dissolve well in water and do not dissolve in organic solvents.

The similar chemical structure of the sulphanilamide drugs explains their common chemical properties and determines their identification reactions. These group reactions are chiefly determined for three functional groups, namely, the aromatic amino and sulpho groups, and the imide group.

Some reactions are a feature of the aromatic nucleus:

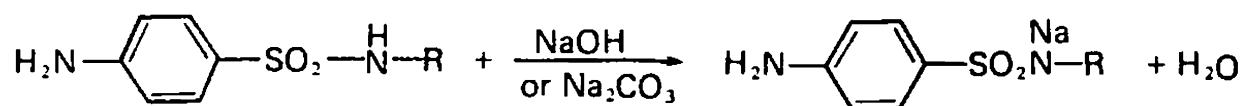


Most sulphanilamides are amphoteric substances having both acidic and basic properties. The latter are due to the presence of an amino group in the aromatic ring. Like a base, they can dissolve in acids with the formation of salts:



Their salts are strongly hydrolyzed in aqueous solutions, however, and do not virtually exist.

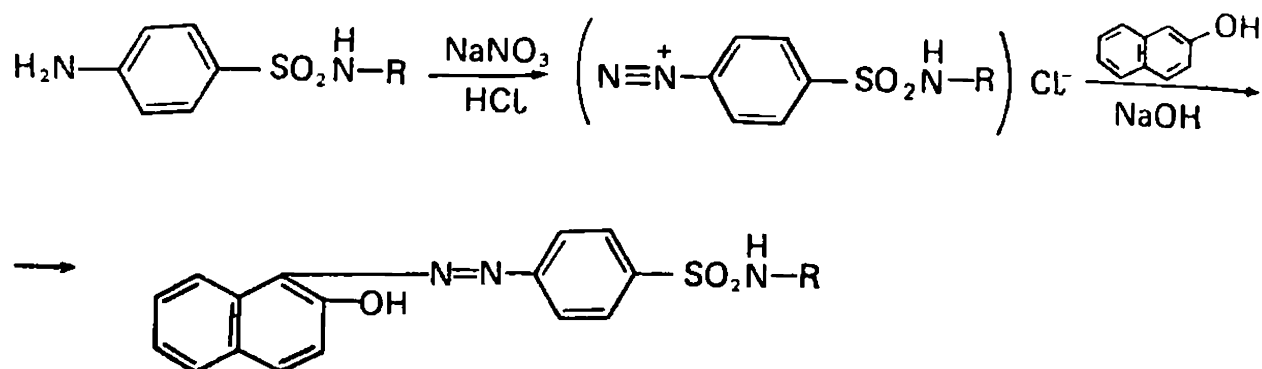
The acidic properties of the sulphanilamides are due to the presence of the imide group hydrogen. The latter can be substituted by metals with the formation of salts. Consequently, most sulphanilamide drugs readily dissolve both in alkalies and in carbonates:



The acidic properties of the sulphanilamides are more pronounced than the basic ones.

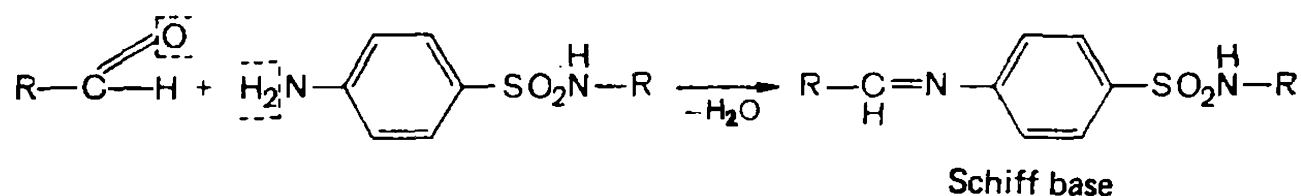
The following reactions can be employed to identify sulphanilamides:

1. Reactions due to the aromatic amino group: (a) the reaction of diazotization and azo combination with phenols (a reaction of the State Pharmacopoeia); when a sulphanilamide is reacted with sodium nitrite in an acidic medium, a diazonium salt forms which in combination with phenol in an acidic medium forms an azo dye:

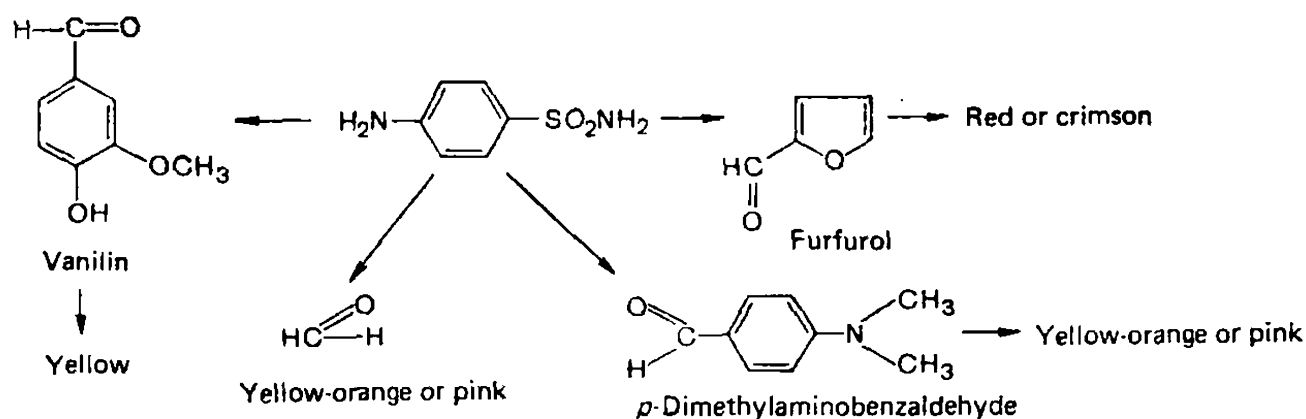


Sulphanilamides with a substituted amino group, for example, soluble streptocid, phthalazole, and phthazine, give this reaction after preliminary hydrolysis has been carried out by heating with dilute hydrochloric acid;

(b) a condensation reaction with aldehydes (the formation of coloured Schiff bases—an unofficial reaction); sulphanilamide drugs, like other aromatic amines, form coloured condensation products of the Schiff base type with many aldehydes, which is widely employed in pharmaceutical analysis for the identification of aromatic amines. The reaction proceeds in an acidic medium:

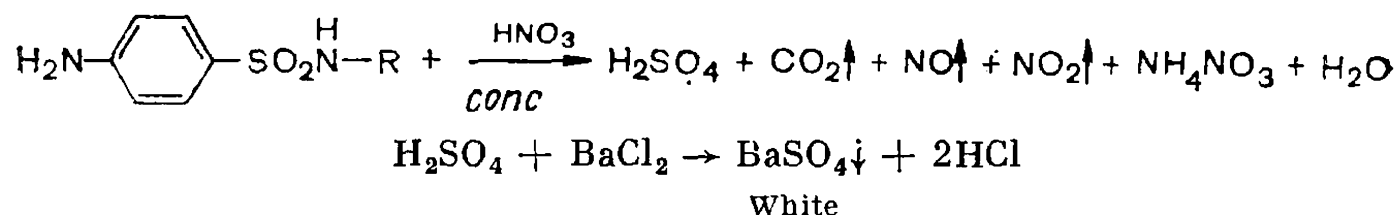


The colour of the condensation products varies depending on the nature of the aldehyde reacting with the sulphanilamide:



A drop reaction very convenient for control at a pharmacy is based on the same principle of condensation of an aromatic amino group with aldehydes: a minute particle of the analyte sulphanilamide or other aromatic amine such as anesthesin (benzocaine) and novocaine (procaine) is placed on paper containing lignin (e.g., wrapping paper), and one drop of dilute hydrochloric acid is added. A yellow-orange colour appears characterizing the product of condensation of an aromatic amine with the aldehydes contained in the lignin.

2. Reactions due to the sulpho group. All the sulphanilamide drugs contain sulphur of a sulphonamide group. To detect it, the organic part of the molecule has to be oxidized with concentrated nitric acid. This causes the sulphur to be converted to sulphate sulphur, which can readily be detected with a barium chloride solution:

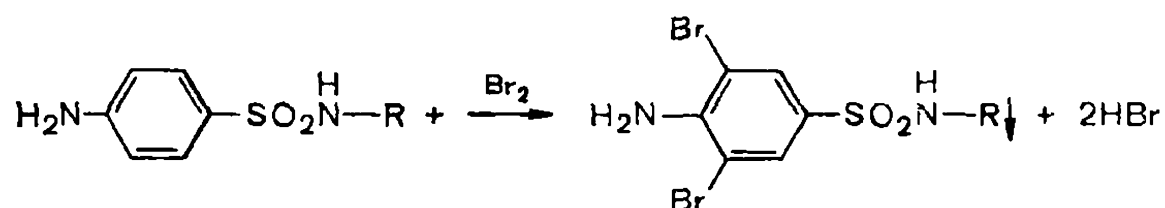


3. Reactions due to the imide group ($-\text{NH}$). The hydrogen of this group provides the possibility of reaction of sulphanilamides with salts of the heavy metals (CuSO_4 , CoCl_2 , etc.). The products are coloured substances either soluble or insoluble in water. The colour of the precipitate or solution is different for each sulphanilamide drug, which makes it possible to distinguish one drug from another. The latter circumstance characterizes this reaction as a specific one. But since all the sulphanilamide drugs give this reaction, it can also be considered as a general one.

It is presumed that the reaction of sulphanilamides with salts of the heavy metals yields coloured chelate compounds. Salts of iron(III), cobalt, copper, etc. are generally used. The State Pharmacopoeia recommends copper sulphate to distinguish one sulphanilamide from another one.

This reaction is conducted with the sodium salts of the sulphanilamides. This is why a sulphanilamide in the acid form is neutralized with an alkali (NaOH), and then a solution of a heavy metal salt is added. One should avoid an excess of the alkali because a hydroxide of the heavy metal may form and mask the main reaction. This is why the State Pharmacopoeia, for neutralization of the imide group hydrogen, recommends an experimentally established amount of sodium hydroxide necessary for the formation of a sodium salt (for the colour of the products of the reaction of sulphanilamides with heavy metal salts see the description of the individual drugs).

4. Reactions due to the aromatic nucleus. An aromatic nucleus in a sulphanilamide can be halogenated, nitrated, or sulphurized:

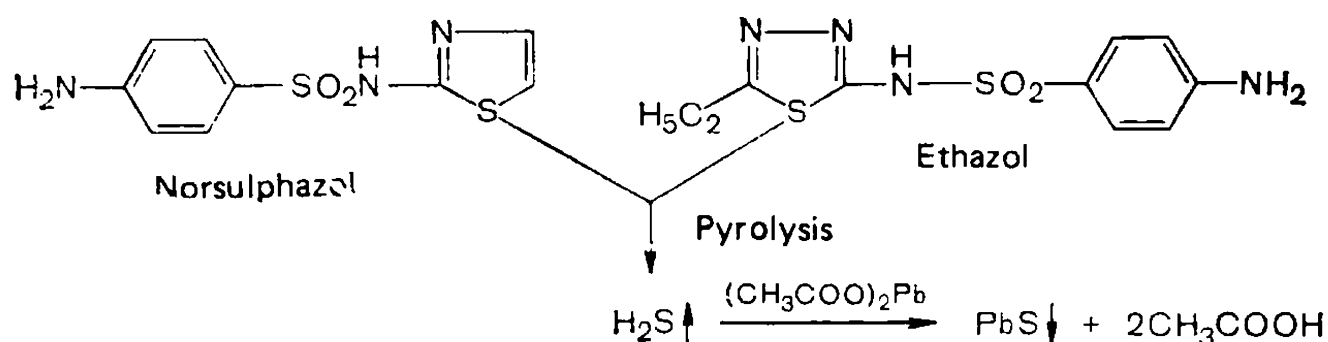


Of significance for pharmaceutical analysis are the nitro derivatives of the sulphanilamides because they are coloured yellow and the bromine derivatives because they are insoluble in water and precipitate.

5. All the sulphanilamides can be thermally decomposed—pyrolyzed. In thermal decomposition, i.e. when a dry powder of these drugs is heated, various crystalline sublimates and melts form. They are generally coloured dark brown. Exceptions are streptocid, sulgin (sulphaguanidine), and urosulphan (sulphacarbamide), whose melts have a violet-red colour. This reaction is a group one for all the sulphanilamides, but at the same time it is a specific one because in a number of cases the colour of the melt is individual for a drug.

If a heterocyclic nucleus of a drug, for example, norsulphazol (sulphathiazole), phthalazole (phthalylsulphathiazole), and ethazol

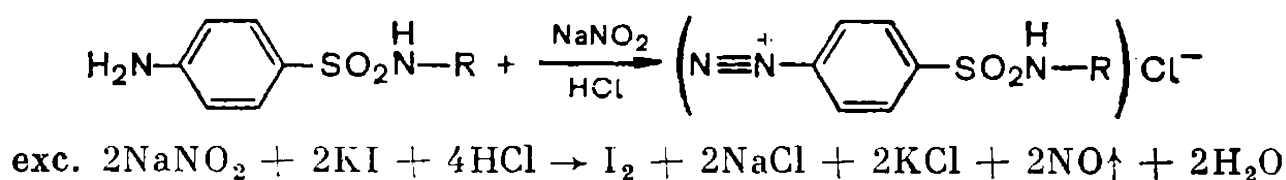
(sulphaethidole) contains sulphur, in its pyrolytic decomposition a gaseous product evolves, in the given case H_2S . It can be determined by its smell or by the blackening of filter paper wetted with a lead acetate solution, the cause of this being PbS :



In the pyrolysis of sulphanilamide drugs containing no sulphur in the nucleus, such as sulphadimezine (sulphadimidine) and sulpha-cyl (sulphacetamide), sulphur dioxide ($\text{SO}_2\uparrow$) forms.

The structure of the sulphanilamides and their specific reactions are chiefly determined by the nature of the radicals R and R' .

The methods used for the quantitative determination of the sulphanilamide drugs are based on their chemical properties and the nature of the functional groups. The official group method for the quantitative determination of sulphanilamide drugs is that of nitritometry. This method uses the ability of the sulphanilamides to become diazotized. Sodium nitrite is used as the standard titration solution. The end of titration is established either with the aid of an external indicator (an iodine-starch paper), or with the aid of an internal one (tropeolin-00), or potentiometrically:



Other methods can be used for the quantitative determination of sulphanilamide drugs in addition to the official one:

(a) neutralization with an alkali; sulphanilamides exhibit acidic properties because of the presence of the imide group hydrogen. The acid forms of the sulphanilamides are titrated in an alcohol medium with an alkali (NaOH) using a thymolphthalein indicator:

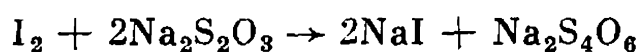
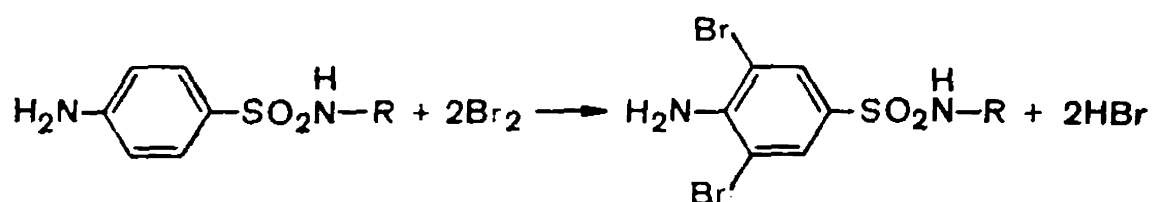
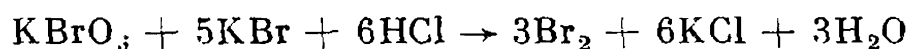


The sodium salts of the sulphanilamides such as sulphacyl sodium (sulphacetamide sodium) are titrated with an acid in an alcohol

acetone medium in the presence of methyl orange:



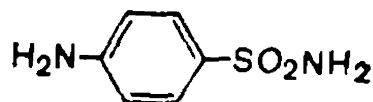
(b) the bromatometric method in which sulphanilamides are halogenated. Potassium bromate is the titration solution, and titration is conducted in an acidic medium in the presence of potassium bromide. The excess of bromine is determined iodimetrically:



(c) the photolorimetric method based on the ability of the sulphanilamides to yield coloured products in reactions with aldehydes and salts of the heavy metals. Azo dyes can also be employed for this method. By comparing the colour intensity with that of a reference solution, one can estimate the content of the substance in the drug.

Streptocid (*Streptocidum*)

para-Aminobenzenesulphamide



$\text{C}_6\text{H}_8\text{N}_2\text{O}_2\text{S}$

M.m. 172.21

All the group reactions characteristic of the sulphanilamides can be used for streptocid (sulphanilamide). The specific reactions identifying the drug include the following:

(a) when heated with an alkali (NaOH), a smell of ammonia is felt (the sulphamide group):

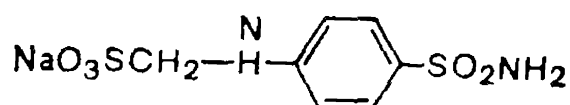


(b) when heated in a dry test tube with the flame of a burner, a violet-blue melt forms and a smell of aniline and ammonia is felt.

The drug is used to treat tonsillitis, erysipelas, and other coccal infections. It is administered orally or externally in the form of an ointment or emulsion. It is dispensed in 0.3- and 0.5-g powders and tablets. A shortcoming of streptocid is its poor solubility in water, therefore streptocid soluble in water was synthesized.

Soluble Streptocid (*Streptocidum solubile*)

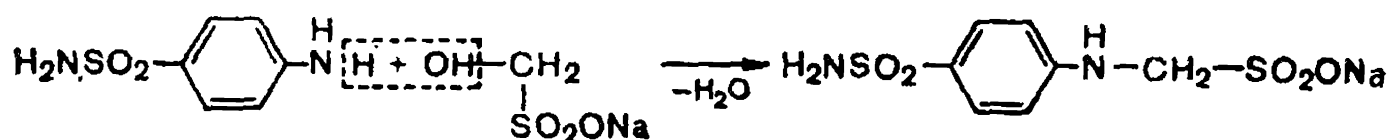
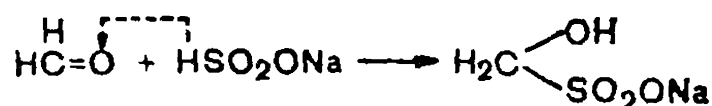
Sodium para-sulphamidobenzeneaminomethanesulphate



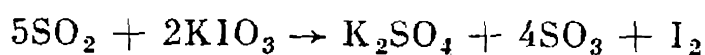
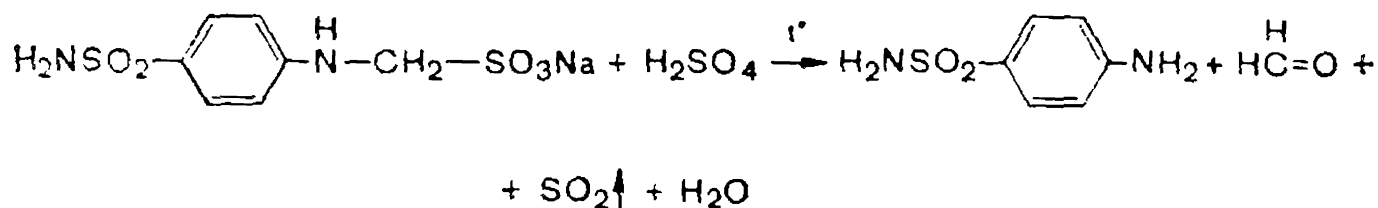
$\text{C}_7\text{H}_9\text{N}_2\text{NaO}_5\text{S}_2$

M.m. 288.28

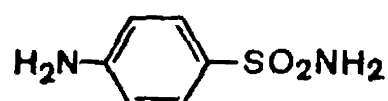
Soluble streptocid is produced by condensing streptocid with a bisulphite derivative of formaldehyde:



Unlike streptocid, this drug colours a burner flame yellow (Na^+). When the drug is heated with concentrated sulphuric acid in the presence of salicylic acid, a cherry red colour appears because of the condensation of the evolving formaldehyde with the salicylic acid (see the reactions of formaldehyde identification, p. 171). Simultaneously, the evolving sulphur dioxide can be detected by the evolution of iodine if potassium iodate is added to the reaction mixture:



When a solution of the drug is boiled with dilute hydrochloric acid, *para*-aminobenzenesulphamide evolves:



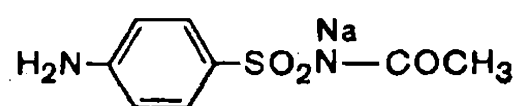
When a sodium nitrite solution and an alkaline solution of 2-naphthene is added, the product is an azo dye of a cherry red colour.

The State Pharmacopoeia recommends determining the content of the drug after saponification by nitritometry.

The good solubility in water makes it possible to use the drug for subcutaneous and intramuscular injections (1-1.5% solutions) and for intravenous ones (2-5-10% solutions). It is dispensed in a powder.

Sulphacyl Sodium (*Sulfacylum-natrium*)

para-Aminobenzenesulphanilacetamide-sodium



$C_8H_9N_2NaO_3S \cdot H_2O$

M.m. 254.24

Sulphacyl sodium (sulphacetamide sodium) dissolves well in water. Its solutions are only slightly alkaline, which allows this drug to be used in the form of injections and eye drops.

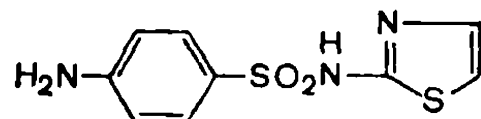
The drug gives all the reactions characteristic of the sulphanilamide preparations. A specific reaction is the saponification of the drug (an odour of acetic acid), and also colour reactions with solutions of salts of the heavy metals. For example, a reaction with a copper sulphate solution yields a precipitate of a light blue-green colour that does not change when the solution is left standing (a distinction from the other sulphanilamide preparations).

The content of the drug is determined by nitritometry relative to the aromatic amino group (State Pharmacopoeia) or by other methods characteristic of the sulphanilamides.

It is administered in solutions and ointments (10-20-30%).

Norsulphazole (*Norsulfazolum*)

2-(para-Aminobenzenesulphamido)-thiazole



$C_9H_9N_3O_2S_2$

M.m. 255.32

As can be seen from its structure, norsulphazole (sulphathiazole) is a sulphanilamide derivative in which one hydrogen atom of the amide group has been substituted by a thiazole ring. The latter has

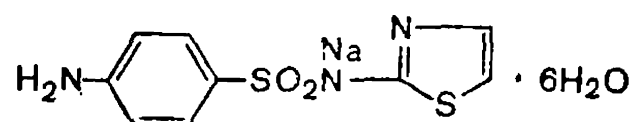
two heteroatoms—sulphur and nitrogen. Such compounds are distinguished by their low toxicity.

Norsulphazole gives all the reactions characteristic of the sulphanilamide preparations. Its specific reaction is that with a copper sulphate solution; a precipitate of a dirty violet colour forms. Also deserving notice is the reaction of detecting the sulphide sulphur in the thiazole ring by pyrolysis (a smell of hydrogen sulphide).

It is dispensed in 0.25- and 0.5-g powders and tablets.

Norsulphazole Sodium (*Norsulfazolum-natrium*)

2-(para-Aminobenzenesulphamido)-thiazole-sodium



$C_9H_8N_3Na \cdot O_2S_2 \cdot 6H_2O$

M.m. 385.39

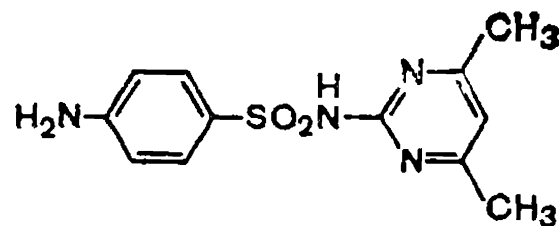
Being a sodium salt, the drug (also called sulphathiazole sodium) differs from norsulphazole in that it dissolves in water and colours the flame of a burner yellow. The other identification reactions are the same as for norsulphazole.

The content of norsulphazole drugs can be determined by one of the methods used for sulphanilamide drugs. Nitritometry is the official method.

The drug is dispensed as a powder. It is administered orally and intravenously in the form of 5% and 10% solutions.

Sulphadimezine (*Sulfadimezinum*)

2-(para-Aminobenzenesulphamido)-4,6-dimethylpyrimidine



$C_{12}H_{14}N_4O_2S$

M.m. 287.33

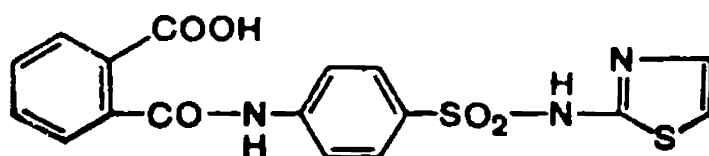
Sulphadimezine (sulphadimidine, sulphamethazine) is identified by the reactions usually employed for sulphanilamide preparations. The specific reaction is the colour one with a copper sulphate solution when a yellowish-green precipitate forms whose colour rapidly changes to brown. This reaction distinguishes sulphadimezine from the other sulphanilamides. Another specific reaction is that with a solution of oxidized sodium nitroprusside (a violet colour).

The content of the drug is determined similarly to the other sulphanilamides.

It is dispensed in 0.25- and 0.5-g powders and tablets.

Phthalazole (*Phthalazolum*)

2-[para-(ortho-Carboxybenzamido)-benzenesulphamido]-thiazole



$C_{17}H_{13}N_3O_5S_2$

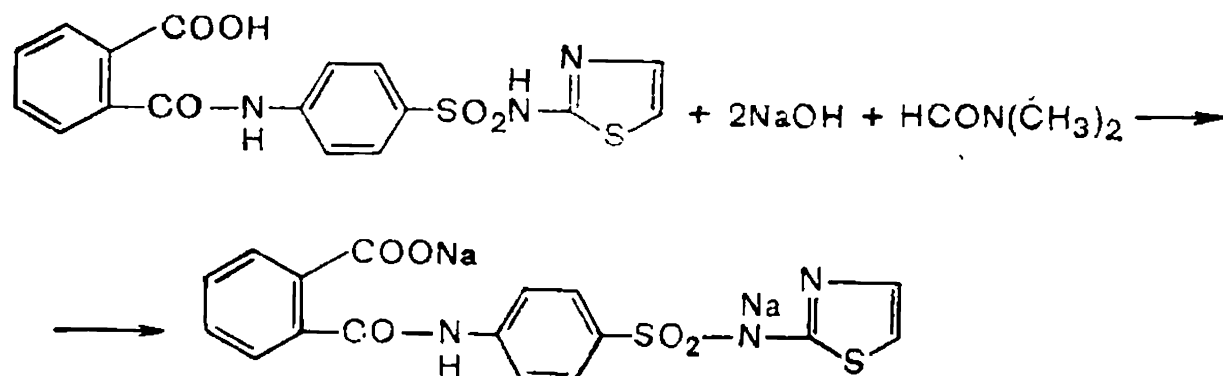
M.m. 403.40

Phthalazole (phthalylsulphathiazole) can be considered as a derivative of norsulphazole in which the hydrogen of the amino group in position 4 has been substituted by a phthalic acid residue. Therefore, unlike other drugs, phthalazole gives a reaction specific for aromatic amines (the formation of an azo dye) only after hydrolysis by hydrochloric acid.

The phthalic acid residue in the phthalazole molecule is confirmed by a bright green fluorescence of the solution after the drug has been melted with resorcinol in the presence of concentrated sulphuric acid and when a dilute alkali solution is added to the cooled melt (see the reactions of identification of resorcinol, p. 221).

In accordance with the way of producing phthalazole, it may contain admixtures of phthalic acid and norsulphazole. The State Pharmacopoeia establishes the tolerated limit of free phthalic acid. The admixture of norsulphazole is determined quantitatively by nitritometry. Its content in the drug must not exceed 0.5%.

The content of the drug is determined by acid-base titration in non-aqueous media. Dimethylformamide neutralized in the presence of a thymol blue indicator is used as the non-aqueous solvent. A 0.1 *N* sodium hydroxide solution in a mixture of methanol and benzene is the titrant. Titration is conducted until a blue colour appears (methyl blue is the indicator):

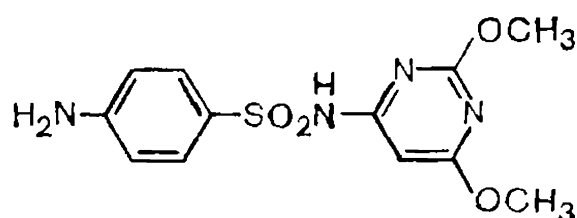


Phthalazole is highly effective with respect to the intestinal flora. The drug is mainly retained in the intestines, where the active sulphonamide part of the molecule is detached and exhibits its antibacterial action. The high sulphonamide concentration in the intestines explains the high effectiveness of the drug.

It is dispensed in 0.5-g powders and tablets.

Sulphadimethoxine (*Sulfadimethoxinum*)

4-(*para*-Aminobenzenesulphamido)-2,4-dimethoxypyrimidine



$C_{12}H_{14}N_4O_4S$

M.m. 310.34

This drug was first produced in Austria (1953). It has a prolonged action. The drug was synthesized in the USSR in 1961.

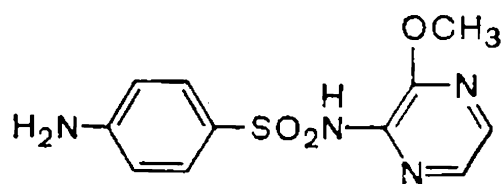
The drug can give all the reactions typical of the sulphanilamides. A specific reaction is that with a solution of cobalt chloride $CoCl_2$, when a bright pink amorphous precipitate with a lilac tint forms.

The content of the drug can be determined by one of the methods characteristic of the sulphanilamides. Nitritometry is the official method.

It is dispensed in 0.2- and 0.5-g tablets.

Sulphalene (*Sulfalenum*)

2-(*para*-Aminobenzenesulphamido)-3-methoxypyrazine



$C_{11}H_{12}N_4O_3S$

M.m. 280.31

Sulphalene is similar to the other sulphanilamides in its antibacterial action, but differs from them in its superprolonged effect, which is its main merit.

Sulphalene is a white odourless crystalline powder. Sometimes it has a yellowish tint. The drug is insoluble in water, sparingly soluble in 95% alcohol and chloroform, dissolves with difficulty in metha-

nol, and readily in a solution of sodium hydroxide and dilute hydrochloric acid (an amphoteric substance).

It is identified by:

(a) a reaction of formation of an azo dye having a cherry-red colour with an orange-red precipitate;

(b) a reaction with a copper sulphate solution; the solution acquires a dirty green colour transforming into a greenish blue one (its distinction from the other sulphanilamides).

The ultraviolet spectrum of a 0.001% solution of the drug in a 0.1 *N* sodium hydroxide solution in the region from 230 to 340 nm has an absorption minimum at 250 ± 2 nm and a maximum at 318 ± 2 nm.

The quantitative determination of the sulphalene in a preparation is performed by nitritometry and other methods that can be employed for the sulphanilamides.

It is stored in a well closed container. Its expiration date is five years after production. It is listed in Group B.

REVIEW QUESTIONS

1. What is the essence of the "phenacetin principle"?
2. What is the colour reaction of phenacetin with potassium dichromate in an acidic medium based on?
3. Why is dilute nitric acid used to produce 3-nitro-4-acetoaminophenetol instead of concentrated acid?
4. Compare the pharmacological properties of all the sulphanilamide drugs and indicate the features of each of them. Explain your comments from a chemical viewpoint.
5. What chemical compounds do most sulphanilamide drugs belong to?
6. What are the amphoteric properties of the sulphanilamides due to?
7. Why do the sulphanilamides dissolve in hydroxides and carbonates?
8. Which part of a sulphanilamide molecule is responsible for halogenation, nitration, and sulphurization?
9. Which functional group in sulphanilamides is responsible for diazotization?
10. Can the sulphur in sulphanilamide drugs be detected in the conventional analytical way?
11. How can the ability of sulphanilamide drugs to react with salts of heavy metals be explained?
12. Why is the pyrolysis of the sulphanilamides employed when conducting particular (individual) reactions?
13. What underlies the method of nitritometry (in the quantitative determination of sulphanilamide drugs), neutralization, photolorimetry, iodochlorimetry, and bromatometry?
14. What are the advantages of soluble streptocid over the insoluble drug?
15. Why is phthalazole hydrolyzed before conducting identification reactions?
16. List the advantages of sulphanilamide drugs with a prolonged action over those with a brief action.

PRACTICAL LESSON

Analysis of a Mixture of Acetylsalicylic Acid and Phenacetin Taken in Equal Parts

1. Write the prescription in Latin.
2. Perform identification reactions:
 - (a) for acetylsalicylic acid: boil about 0.02 g of the mixture with 3 ml of a sodium hydroxide solution and after cooling the solution acidify it with dilute sulphuric acid; a white crystalline precipitate forms and a smell of acetic acid is felt;
 - (b) for phenacetin: dissolve about 0.02 g of the mixture in 1 ml of hydrochloric acid, boil the solution during one minute, cool it, and add two drops of a potassium dichromate solution; a blue-violet colour forms;
 - (c) dissolve about 0.02 g of the mixture in 1-2 ml of dilute nitric acid, agitate and slightly heat the solution; a yellow precipitate forms. Write the equations of the chemical reactions.
3. Conduct a quantitative determination (by the neutralization method): transfer 0.1 g of the mixture into a flask for titration, dissolve it in 3 ml of alcohol, add 5 ml of water, two drops of phenolphthalein, and titrate with a 0.1 *N* sodium hydroxide solution up to a pale pink colour. Write the equation of the chemical reaction.
4. Calculate the content of the acetylsalicylic acid in the powder in grammes by formula (1.3):

$$X = \frac{VK Tb}{a} = \frac{VK \times 0.01802 \times 0.1}{0.1} = VK \times 0.01802$$

where *V* is the volume of the 0.1 *N* sodium hydroxide solution, ml, *T* = 0.01802 g/ml, *a* is the mass of the drug sample, g, and *b* is the mass of one powder, g.

The phenacetin content is found as the difference between the mass of one powder (in the given case 0.1 g) and the mass of the acetylsalicylic acid found after titration (0.1 — *X*).

5. Compare the result with the doctor's prescription and determine whether the given medicinal form can be dispensed to the patient.

Analysis of a 20% Sulphacyl Sodium Solution

1. Write the prescription in Latin.
2. Perform identification reactions:
 - (a) to several drops of the analyte solution add several drops of a solution of sodium nitrite and hydrochloric acid. Add one drop of the obtained diazonium salt to 1 ml of an alkaline solution of 2-naphthol; a cherry-red colour appears;
 - (b) to several drops of a solution of the drug add several drops of a copper sulphate solution; a light blue-green colour appears that does not change when the solution is left in the air.
- Write the equations of the chemical reactions.
- Conduct a quantitative determination (by the neutralization method): place 5 ml of the analyte solution into a conical flask for titration, add three drops of methyl orange, and titrate with a 0.1 *N* solution of hydrochloric acid until the colour of the indicator changes. Write the equation of the chemical reaction.

4. Evaluate the sulphacyl sodium content in the solution in per cent by formula (1.1):

$$X = \frac{VKT}{a} \times 100 = \frac{VK \times 0.0254}{5.0} \times 100$$

where V is the volume of the 0.1 N hydrochloric acid solution, ml, $T = 0.0254$ g/ml, and a is the volume of the drug taken for titration, ml.

5. Compare the result with the doctor's prescription and make the relevant conclusion.

Analysis of Norsulphazole (Sulphathiazole)

1. Perform identification reactions:

(a) dissolve a small amount of the drug in water acidified with dilute hydrochloric acid, and add one or two drops of a sodium nitrite solution. Add one drop of the obtained diazonium salt to 1 ml of an alkaline solution of 2-naphthol; a cherry-red colour appears;

(b) agitate a small amount of the drug with a 0.1 N sodium hydroxide solution and add 1 ml of a copper sulphate solution; a dirty violet colour appears;

(c) heat a small amount of the drug in a dry test tube—a dark brown melt forms and a smell of hydrogen sulphide is felt.

Write the equations of the chemical reactions.

2. Conduct a quantitative determination (by the nitritometric method): transfer 0.1 g of the drug into a conical flask for titration, add 10 ml of dilute hydrochloric acid and 5 ml of water. Shake the flask until the sample dissolves. Add 25 ml more of water, 0.35 g of crystalline potassium bromide, and titrate with a 0.1 M sodium nitrite solution using tropeolin-00 as the indicator (four drops) until the colour changes from red to yellow. Write the equations of the chemical reactions.

3. Find the norsulphazole content in the drug in per cent by formula (1.1):

$$X = \frac{VKT}{a} \times 100 = \frac{VK \times 0.02553}{0.1} \times 100$$

where V is the volume of a 0.1 M sodium nitrite solution, ml, $T = 0.02553$ g/ml, and a is the mass of the drug, g.

The State Pharmacopoeia requires that the content of $C_9H_9N_3O_2S_2$ be at least 99.0%.

4. Compare your result with the official requirements and conclude whether the drug may be dispensed.

5. What other methods can be used for the quantitative determination of norsulphazole. Give a chemical substantiation.

Analysis of a 2% Streptocid Ointment

1. Write the prescription in Latin.

2. Perform a quantitative determination (the bromatometric method): place 0.5 g of the ointment weighed on parchment paper into a flask for titration, add 5 ml of chloroform, shake the flask until the ointment dissolves, next add 5 ml of 2 N sulphuric acid, 0.1 g of potassium bromide, two drops of methyl orange, and titrate with a 0.1 N potassium bromate solution with vigorous shaking until the pink colour disappears. Write the equations of the chemical reactions.

3. Calculate the streptocid content in the ointment in per cent by formula (1.1):

$$X = \frac{VK T}{a} \times 100 = \frac{VK \times 0.05166}{0.5} \times 100$$

where V is the volume of the 0.1 N potassium bromate solution, ml, $T = 0.05166$ g/ml, and a is the mass of the ointment sample, g.

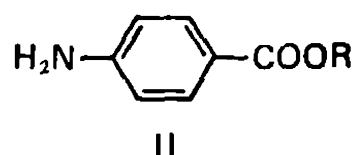
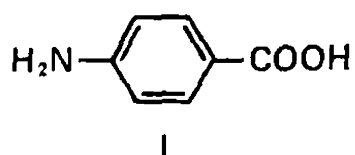
4. Compare the result with the prescription and arrive at the relevant conclusion.

5. Propose a different procedure and identification reaction for streptocid in streptocid ointment. Write the equations of the chemical reactions.

Chapter 24. Aromatic Amino Acids, Amino Alcohols, and Their Derivatives

24.1. AMINO ACID DERIVATIVES

Aminobenzoic acid is the simplest amino acid of the aromatic series. Of its three possible isomers, of interest for medicine is para-aminobenzoic acid (I) whose esters (II) exhibit a physiological activity and are employed as local anaesthetics:



The natural alkaloid cocaine used in medicine as a drug with a local anaesthetic action could not meet medicinal requirements because of its shortcomings. The main shortcomings of cocaine are:

(1) habituation to the drug, which results in the development of drug addiction;

(2) a high toxicity;

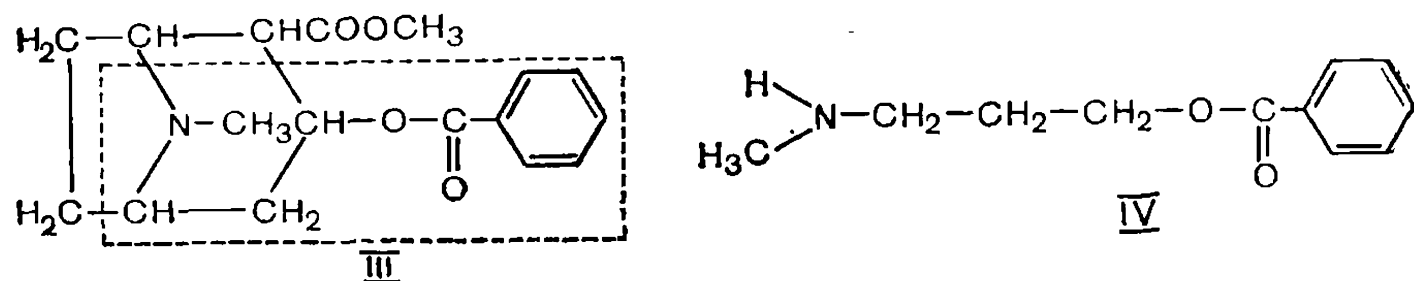
(3) the scarcity of the natural source of cocaine because the coca shrubs from whose leaves it is produced grows only in definite climatic zones, hence cocaine for many countries is an imported and very costly drug;

(4) the content of cocaine in the coca leaves is very low, which increases the cost of producing this drug.

All these shortcomings made it necessary to search for other, synthetic drugs having a local anaesthetic action. This led to the synthesis of *para*-aminobenzoates.

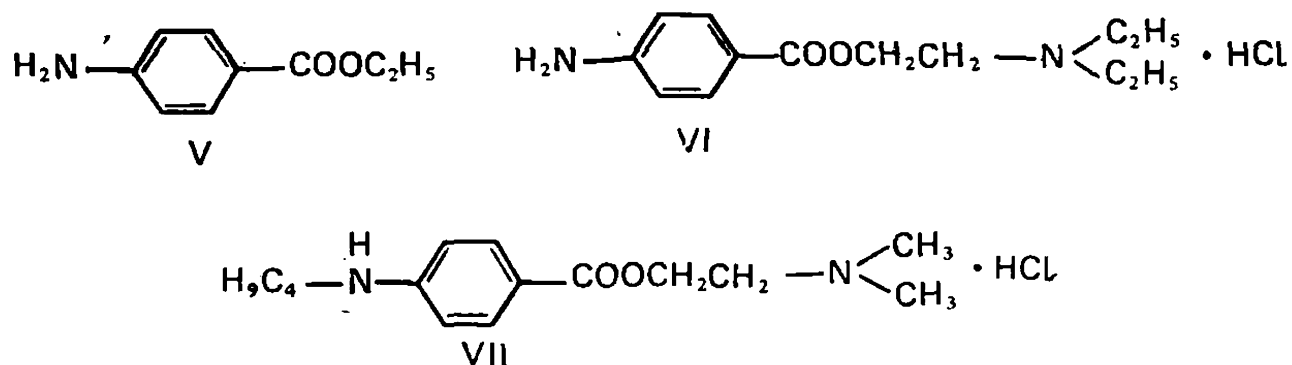
Studying of the structure of natural cocaine (III) revealed that only a certain part of the cocaine molecule exhibits an anaesthetic

action. This part is an ester of benzoic acid and an amino derivative of propanol (IV):



Investigations showed that such benzoates have a stronger anaesthetic effect than cocaine, but they cause irritation. It was later found that this shortcoming is absent in the esters of *para*-aminobenzoic acid, which retain the same physiological effect.

Thus, there was created a group of synthetic local anaesthetics, i.e. esters of *para*-aminobenzoic acid. The main drugs of this group are anesthesin (benzocaine) (V), novocaine (procaine) (VI), and dicaine (tetracaine) (VII). All these drugs are pharmacopoeial ones:



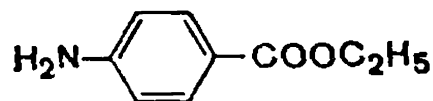
An advantage of these compounds over cocaine is that they are simple in structure and readily synthesized, are less toxic, do not cause habituation, and give no side effects. An exception is dicaine, whose toxicity exceeds that of cocaine ten times.

The esters of *para*-aminobenzoic acid have a similar structure, and exhibit a number of group reactions such as the formation of an azo dye via the free amino group in the aromatic ring; having an aromatic ring, they can be brominated, nitrated, and sulphurized. These group reactions also underlie the methods used for their quantitative determination, such as nitritometry, bromatometry, and the colorimetric method (see Chap. 23).

In addition to the group reactions, there is a particular, specific reaction for each drug determined by the functional groups in a molecule.

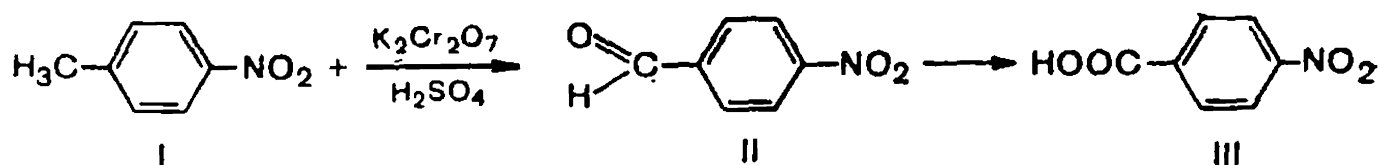
Anesthesin (*Anaesthesinum*)

Ethyl para-aminobenzoate

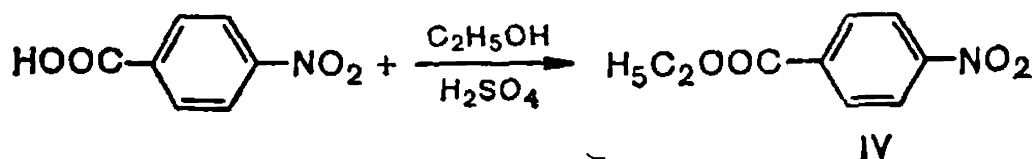

$$\text{C}_9\text{H}_{11}\text{NO}_2$$

M.m. 165.19

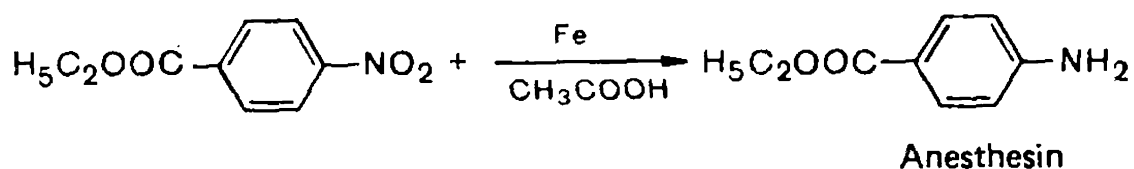
The production of anesthesin (benzocaine, ethoform, norcaine) can be represented by the following scheme: *para*-nitrotoluene (I) is oxidized by potassium dichromate to *para*-nitrobenzaldehyde (II), and then to *para*-nitrobenzoic acid (III):



This acid is esterified with ethanol in the presence of sulphuric acid:



The ethyl ester of *para*-nitrobenzoic acid (IV) is reduced by iron shavings in the presence of acetic acid CH_3COOH (a weak organic acid is used to prevent saponification of the ester group):

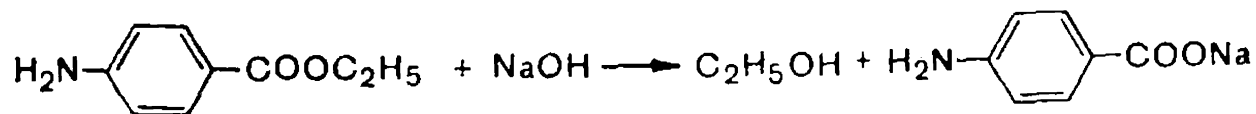


Anesthesin

To purify the produced anesthesin, it is recrystallized from an alcohol solution with activated carbon and sodium hydrogen sulphite that decolorize the soluble coloured admixtures.

Pure anesthesin is a white crystalline odourless powder. It has a slightly bitter taste and causes numbness of the tongue. It dissolves readily in ether, chloroform, and alcohol.

A specific reaction for anesthesin is its reaction for ethanol that forms after hydrolysis of the drug in an alkaline solution:



The ethanol is detected by the formation of iodoform after an iodine solution is added (see the reactions of identification of ethanol, p. 164).

Another identification reaction of anesthesin is that of its oxidation by chloroamine in the presence of hydrochloric acid. The product has a reddish-orange colour (owing to the presence of the aromatic amino group) that can be seen more clearly when the mixture is agitated with ether.

The drug may contain chlorides and organic substances as admixtures. A tolerated limit of acidity is also established.

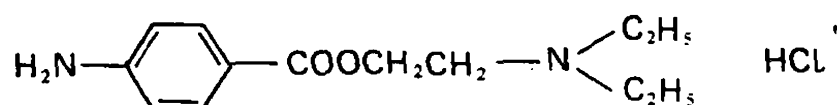
Anesthesin can be determined quantitatively by the following methods: (a) by nitritometry with the indicator consisting of tropeolin-00 mixed with methylene blue (the official method); (b) by bromatometry; (c) by neutralization with saponification of the ester group; and (d) by colorimetry (using an azo dye). All these methods have been described on earlier pages.

Anesthesin is employed as a local anaesthetic both orally and externally. It is administered orally in 0.3-g powders and tablets for anaesthesia of the mucous membranes in gastric neurosis. It is applied externally in the form of a 5-10% ointment or powder in diseases of the skin attended by itching, and also for the anaesthesia of wounds.

It should be stored in well closed jars in a dry place protected from light. It is listed in Group B.

Novocaine (*Novocainum*)

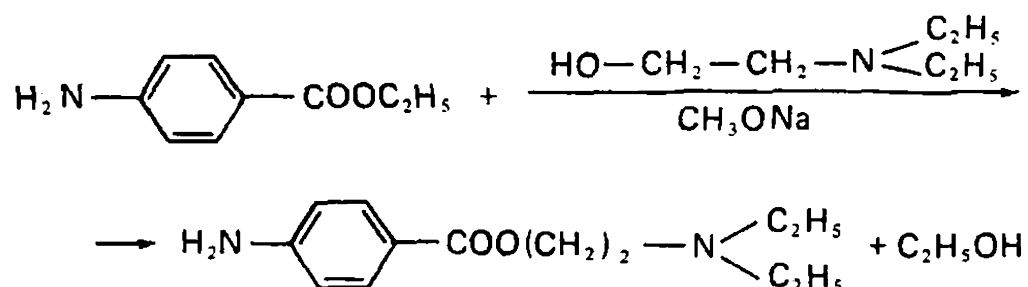
(*Diethylaminoethyl-para-aminobenzoate hydrochloride*)



$\text{C}_{13}\text{H}_{20}\text{N}_2\text{O}_2 \cdot \text{HCl}$

M.m. 272.78

Novocaine (procaine, ethocaine) is synthesized in the simplest and most convenient way by the re-esterification of ethyl *para*-aminobenzoate (anesthesin) with diethylaminoethanol in the presence of a sodium alcoholate (an alcoholysis reaction):



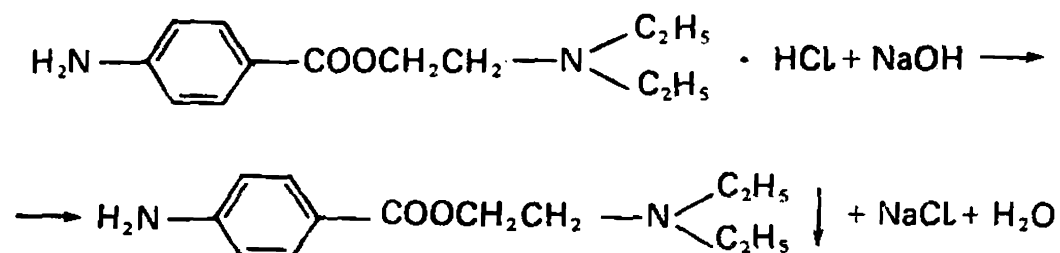
The simultaneously formed ethanol is readily distilled off because its boiling point is considerably lower than that of the diethylamino-ethanol. The obtained base of novocaine is next transformed into the chloride by the action of a calculated amount of an alcohol solution of hydrochloric acid. The diethylamino group in the side chain of the novocaine molecule exhibits stronger basic properties in comparison with the aromatic amino group, and therefore stable water-soluble salts can form with acids.

The solubility of novocaine in water makes possible its use for injections, which is an advantage over anesthesin.

Pure novocaine is an odourless white crystalline powder or colourless crystals. It has a bitter taste and causes numbness of the tongue. The drug dissolves very readily in water. Aqueous solutions of novocaine hydrochloride have an acid reaction.

In addition to the group reactions characteristic of the given group of drugs, the following identification reactions are specific for novocaine:

(a) the separation of the base of novocaine (an oily liquid) when the drug is reacted with an alkali:



(b) the decolorizing of a potassium permanganate solution due to oxidation of the aromatic amino group;

(c) the formation of a white silver chloride precipitate when a solution of the drug is reacted with a silver nitrate solution (a reaction for HCl).

The content of the drug is determined by nitritometry (State Pharmacopoeia) and by other methods typical of *para*-aminobenzoate drugs.

Novocaine can also be determined with respect to the hydrochloric acid by argentometry or neutralization. In the latter case, titration is conducted in the presence of chloroform for extraction of the separated base.

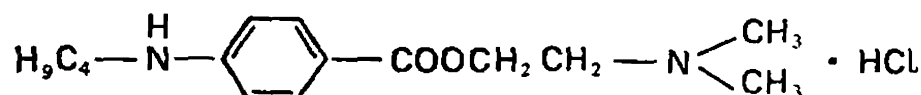
Novocaine is one of the most widely employed local anaesthetics. With a view to the brief action of novocaine, it is often administered together with adrenaline (epinephrine), which owing to its vasoconstrictive action retards the absorption of the novocaine and prolongs the period of its action.

In addition to the crystalline preparation of novocaine, the State Pharmacopoeia describes another preparation—*Solutio Novocaini* 0.25%, 0.5%, 1% aut 2% *pro injectionibus*.

The drug should be stored in well closed orange glass jars. It is listed in Group B.

Dicaine (*Dicainum*)

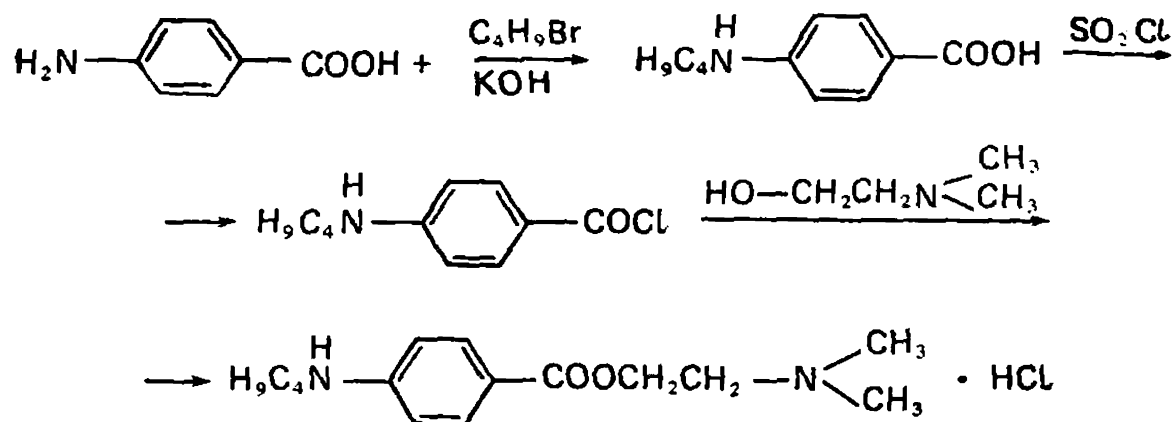
2-Dimethylaminoethyl-para-butylaminobenzoate hydrochloride



$\text{C}_{15}\text{H}_{24}\text{N}_2\text{O}_2 \cdot \text{HCl}$

M.m. 300.83

Dicaine (tetracaine, amethocaine) is produced according to the following scheme: *para*-aminobenzoic acid is heated with *n*-butyl bromide in the presence of an alkali; the produced *para*-butylaminobenzoic acid is reacted with thionyl chloride SO_2Cl , which transforms it into the chloranhydride. The latter is condensed with dimethylaminoethanol:

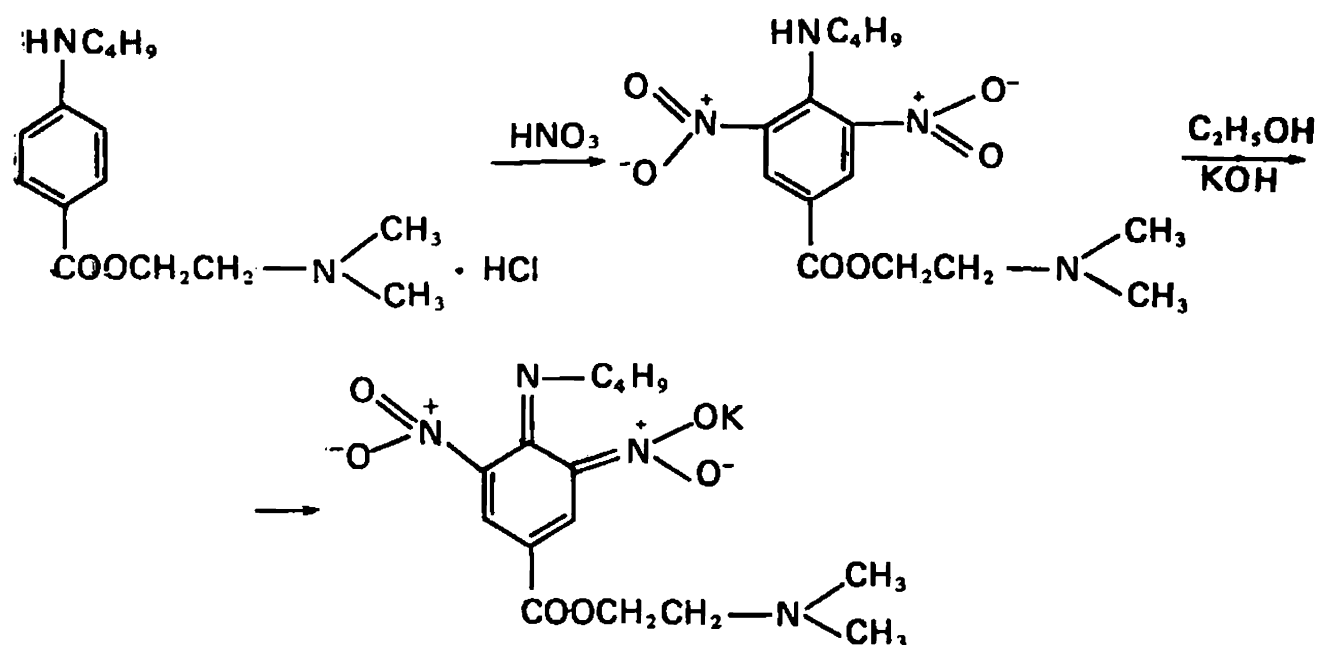


Dicaine is a white odourless crystalline powder. It dissolves readily in water and alcohol, sparingly in chloroform, and is insoluble in ether. Aqueous solutions of dicaine have a neutral reaction, are stable, and do not decompose during sterilization at 100 °C.

A dicaine molecule contains no free aromatic amino group, hence dicaine does not have the reactions inherent in this group (the formation of an azo dye, condensation with aldehydes, etc.).

A specific reaction of dicaine is that with concentrated nitric acid which nitrates the aromatic nucleus, and after the addition of a few drops of an alcohol solution of an alkali (KOH), the resulting salt of

the aciform, which is a quinoid structure, is coloured blood-red:



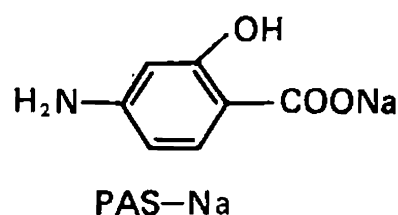
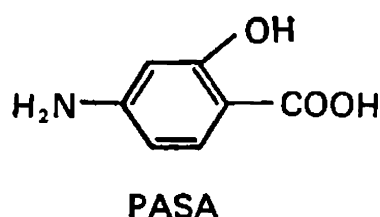
This is the official reaction for identifying the drug. The State Pharmacopoeia also recommends a reaction with ammonium thiocyanide. The formed dicaine thiocyanide precipitates; after recrystallization from water it is dried and its melting point is determined (130-132 °C).

The quantitative determination of the drug is performed by nitritometry after its saponification with an acid (State Pharmacopoeia). Other methods can also be used, for example, the hydrochloric acid is determined by neutralization in the presence of chloroform that extracts the evolving dicaine base.

In its physiological action, dicaine is similar to novocaine, but its activity is much higher. Dicaine is employed together with adrenaline (epinephrine) for surface anaesthesia, chiefly in ophthalmology in the form of 0.25-2% solutions. It is used for anaesthesia in diseases of the ear, throat, and nose in the form of 1-5% solutions. Dicaine has a more prolonged action than novocaine. It is dispensed in powders. The highest single dose for anaesthesia of the upper respiratory tracts is 0.09 g or 3 ml of a 3% solution.

It should be stored in well closed glass jars in a locked cupboard. It is listed in Group A.

In addition to the derivatives of *para*-aminobenzoic acid, the derivative of another aromatic amino acid—*para*-aminosalicylic acid (PASA) is used in medicine. It is employed most frequently in the form of its sodium salt PAS-Na:

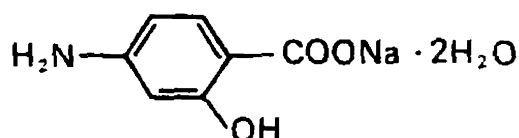


The physiological action of these substances is absolutely different from that of the derivatives of *para*-aminobenzoic acid. They are used as antituberculosis drugs.

Para-aminobenzoic acid is essential for the normal activity of microorganisms, while *para*-aminosalicylic acid, which differs from the former in the presence of a phenol hydroxyl group, participates in metabolism, suppressing the growth of microorganisms, and causes their degeneration. Consequently, PASA is an antagonist of *para*-aminobenzoic acid.

Sodium *para*-Aminosalicylate (*Natrii para-aminosalicylas*)

Sodium salt of para-aminosalicylic acid



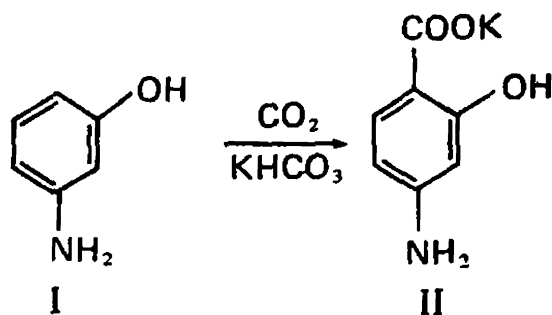
$\text{C}_7\text{H}_6\text{NNaO}_3 \cdot 2\text{H}_2\text{O}$

M.m. 211.15

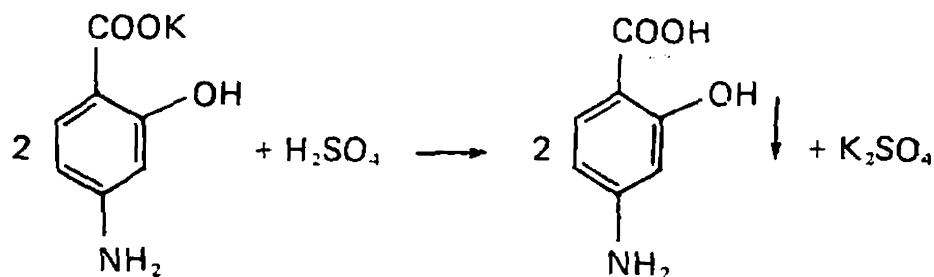
PASA and its sodium salt are produced synthetically. There are many different synthesis methods, but the one developed by a group of scientists of the Latvian SSR Academy of Sciences is the most interesting and is of a commercial significance.

The initial substance for the production of PAS-Na by this method is *meta*-aminophenol (I). The synthesis process consists of three stages.

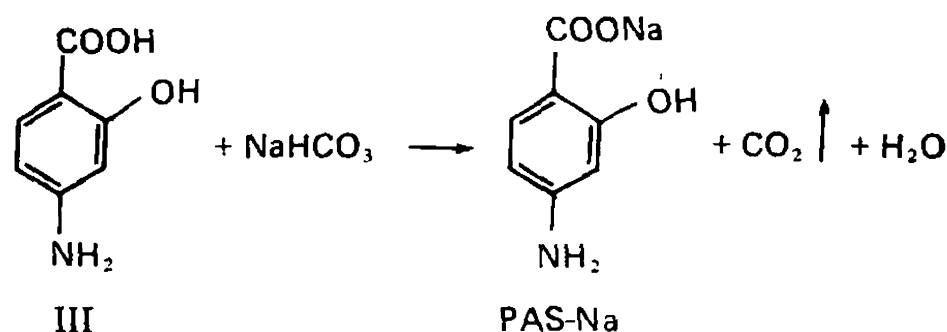
1. The carboxylation of *meta*-aminophenol with carbon dioxide under pressure and at 103-105 °C in the presence of potassium hydrogen carbonate:



2. The separation of PASA by reacting a purified solution of potassium *para*-aminosalicylate (II) with a 50% sulphuric acid solution:

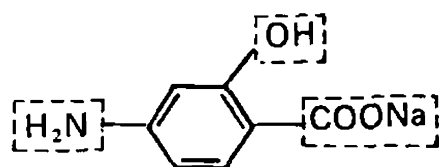


3. The production of sodium *para*-aminosalicylate by neutralizing PASA (III) with sodium hydrogen carbonate:



Sodium *para*-aminosalicylate is a finely crystalline white powder with a yellowish or pinkish tint. It dissolves readily in water and sparingly in alcohol.

The reactions for identifying PAS-Na are carried out relative to three functional groups, namely, an aromatic amino group (see Chap. 23), a phenol hydroxyl group (see Chap. 19), and a carboxyl group (see Chap. 20):



To identify the drug, the State Pharmacopoeia also recommends measurement of the optical density of a 0.001% solution of the drug at wavelengths of 265 and 299 nm. The ratio of the obtained values at the given wavelengths must be within 1.50-1.56.

The drug may contain sulphates, chlorides, and heavy metals within the tolerated limits. The limit of acidity and alkalinity in the drug is also established.

A very undesirable toxic admixture is *meta*-aminophenol. It can be present because it is the starting compound in the synthesis of PAS-Na. This admixture is determined by the reaction of formation of an azo dye when *para*-nitroaniline and sodium nitrite are added in an acidic medium. The resulting colour must not exceed that of a reference solution of *meta*-aminophenol.

The content of the drug can be determined in various ways, namely, by nitritometry (State Pharmacopoeia), neutralization, or bromatometry.

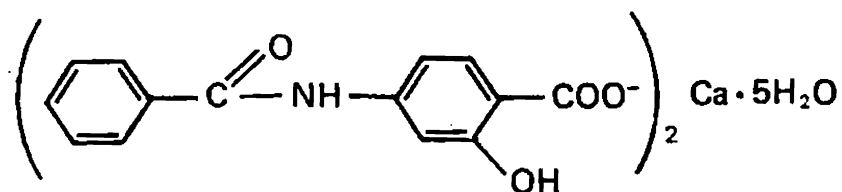
Sodium *para*-aminosalicylate is dispensed in 1-g powders and tablets. It should be stored in well closed jars in a dry place protected from light. PAS-Na has a number of shortcomings:

- (1) a low activity, owing to which the drug is prescribed in large doses, up to 15-20 g a day, which is very inconvenient for a patient;
- (2) undesirable side effects: shiver, nausea, vomiting;
- (3) it causes hypokaliaemia (low blood potassium), therefore it is recommended to administer potassium salts simultaneously with PAS-Na.

All these shortcomings prompted chemists to search for new derivatives of *para*-aminosalicylic acid. One of them that has found use in medicine is the drug bepask.

Bepask (*Bepascum*)

Calcium para-benzoylaminosalicylate



$\text{C}_{28}\text{H}_{20}\text{CaN}_2\text{O}_8 \cdot 5\text{H}_2\text{O}$

M.m. 642.6

Bepask is a Soviet made drug. It was first synthesized at the Moscow Salicylic Plant in the same way as the foreign made drug calcium benzamidosalicylate.

Bepask is a white powder, sometimes with a creamish tint. It is practically insoluble in water and dissolves with difficulty and slowly in ethanol.

Unlike PAS-Na, in a bepask molecule the aromatic amino group is blocked by a benzoic acid residue, therefore it does not give the reactions characteristic of this functional group. The drug is identified by reactions for the phenol hydroxyl group (see Chap. 19) and for the calcium ion (a specific reaction) after the drug has been heated with dilute hydrochloric acid. The resulting soluble calcium chloride CaCl_2 is identified by a reaction with ammonium oxalate (see the reactions of identification of calcium chloride, p. 114). The drug may contain admixtures of chlorides, sulphates, and heavy metals within the limits indicated in the State Pharmacopoeia. The latter requires that the drug contain no admixture of a free amine, which is detected by the reaction of azo dye formation similar to that used for the drug PAS-Na.

The content of the drug is determined by complexometry (relative to Ca^{2+}).

The physiological action of bepask consists in that *para*-aminosalicylic acid, which is what has the healing effect, slowly detaches in an organism from a bepask molecule.

When bepask is employed, the concentration of PASA in the blood becomes constant, and the action of the drug is prolonged, which makes it possible to lower the doses of the drug.

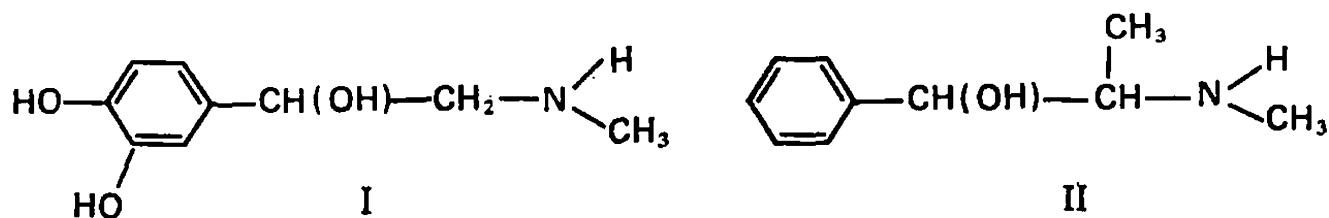
Bepask is combined with streptomycin or isoniazid. It is presumed that bepask retards the inactivation of isoniazid in an organism.

The drug is dispensed in 0.5-g powders and tablets.

It should be stored in well closed containers protecting it from the action of light.

24.2. AMINO ALCOHOL DERIVATIVES

Among the amino alcohol derivatives, adrenaline (epinephrine) (I) and ephedrine (II) are widely used in medicine in the form of their salts:



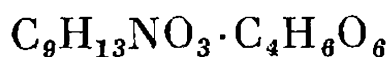
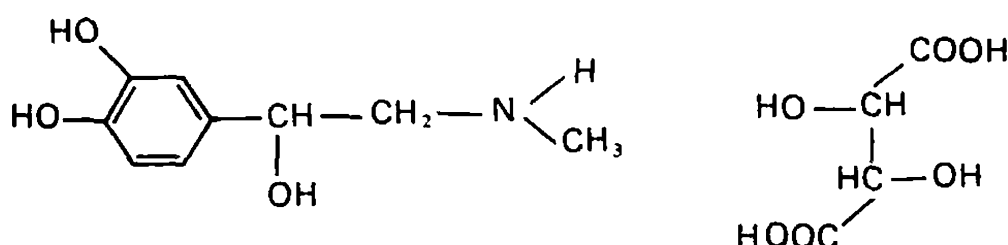
Inspection of their formulas reveals that adrenaline and ephedrine contain a secondary alcohol group (—CHOH) and a partly substituted amino group ($\text{—N} \begin{smallmatrix} \text{H} \\ \diagup \\ \text{CH}_3 \end{smallmatrix}$) in the side chain, and therefore they can be related to secondary amino alcohols of the aromatic series. Unlike ephedrine, adrenaline contains two phenol hydroxyl groups in its molecule in the *ortho*-position (a pyrocatechol derivative), therefore it can be related to the aminophenols. Both substances are of a natural origin.

Adrenaline is a hormone of the adrenal medulla of the adrenal glands, whence it was first separated.

Ephedrine and its isomer pseudoephedrine are substances of a vegetative origin found in various species of *ephedra*. Ephedrine is close to adrenaline in its physiological action. Both drugs have a stimulating effect on the sympathetic nerves (sympathomimetic preparations) and raise the blood pressure, which is associated with their vasoconstrictive action.

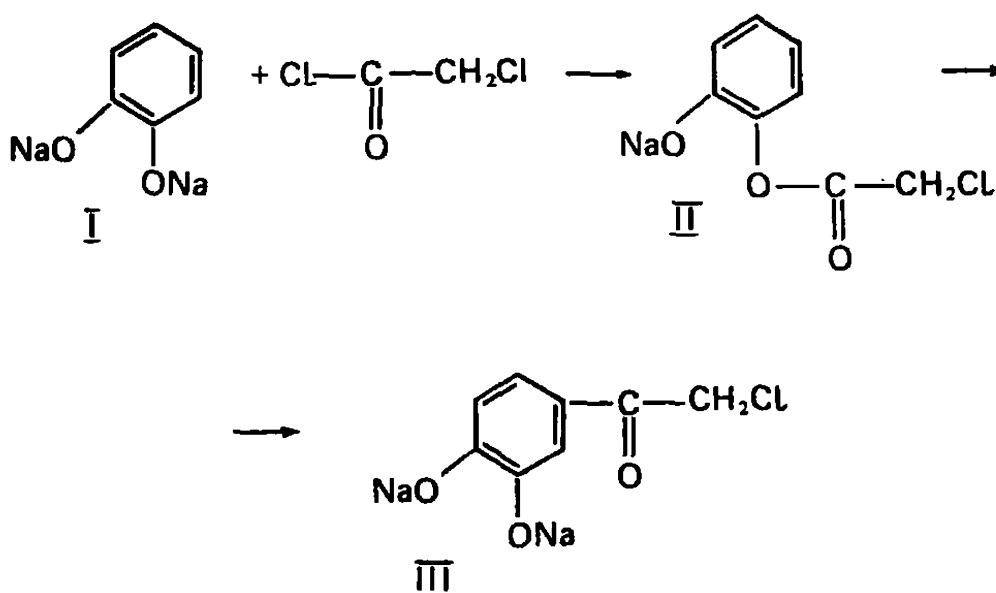
Adrenaline Hydrogen Tartrate (*Adrenalini hydrotartras*)

*l-l-(3, 4-Dihydroxyphenyl)-2-methylaminoethanol
hydrogen tartrate*

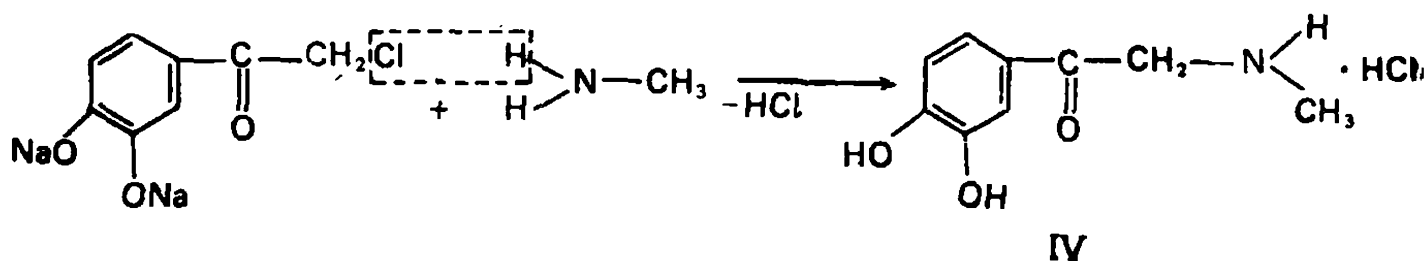


M.m. 333.30

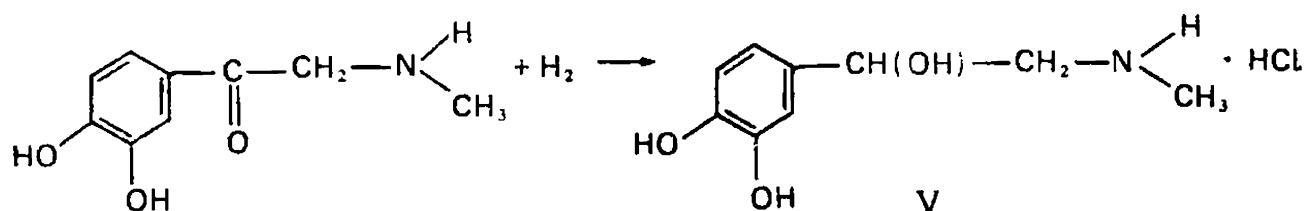
The adrenaline (epinephrine) intended for medicinal purposes is produced synthetically. The starting substance for synthesis is sodium pyrocatechinate (I) which is heated with the chloranhydride of monochloroacetic acid in an alkaline medium. The product is pyrocatechol monochloroacetate (II), which regroups into chloromethyl-dihydroxyphenolketone (III):



The product of the reaction between compound (III) and methylamine is adrenalone, which separates in the form of its hydrochloride (IV):



The reduction of adrenalone yields adrenaline hydrochloride (V):



Adrenaline is optically active. The natural substance is a levorotatory isomer, and the synthetic substance is a racemate. After treatment of the adrenaline racemate with tartaric acid, a mixture of the levorotatory and dextrorotatory hydrogen tartrates is obtained that can be separated by taking advantage of their different solubility in alcohol. The levorotatory isomer of the hydrogen tartrate dissolves poorly in alcohol and crystallizes out of the solution, while the dextrorotatory isomer remains in the solution.

In medicine, the levorotatory synthetic isomer of adrenaline hydrogen tartrate is employed; it is completely identical to the natural levorotatory isomer.

Simultaneously with adrenaline, its analogue noradrenaline (norepinephrine, levarterenol) was produced; it differs from adrenaline only in the absence of the methyl group at the nitrogen atom in the side chain. In an organism, noradrenaline transforms into adrenaline.

The official drugs of these two hormones are their salts with tartaric acid. Adrenaline hydrogen tartrate is a white crystalline powder, sometimes with a slightly grayish tint, without an odour. It changes under the action of light and the oxygen of the air. It dissolves readily in water, slightly in alcohol, and is insoluble in ether and chloroform.

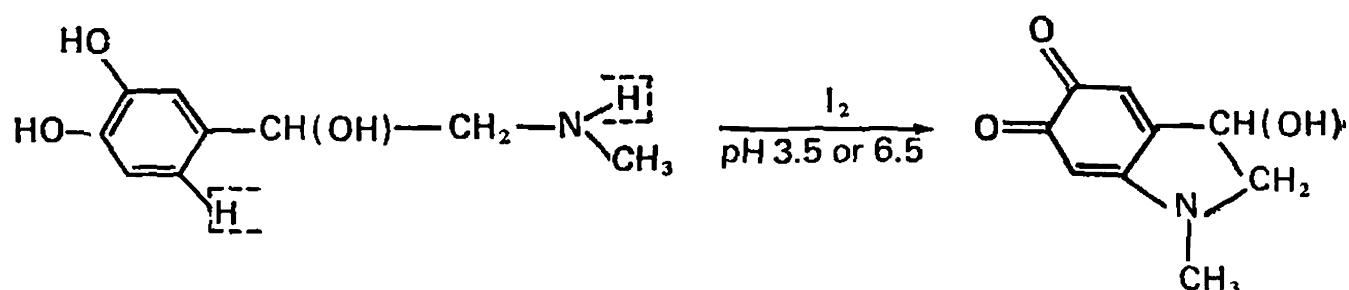
Adrenaline has a nucleus of a diatomic phenol, i.e. pyrocatechol in its molecule and can be readily oxidized, being at the same time a reducing agent. It reduces silver from an ammonia solution of silver nitrate and free copper from red copper(I) oxide. This preparation is oxidized especially readily in an alkaline medium.

The drug is identified by:

(a) a reaction with an iron(III) chloride solution; adrenaline reacts with an iron chloride solution to form an emerald green colour, which turns cherry-red, and then orange-red when a drop of an ammonia solution is added.

(b) oxidation with an iodine solution (the formation of a coloured adrenochrome); when an iodine solution is added to a solution of the drug in the presence of a hydrogen tartrate buffer solution with a pH of 3.56, a dark red adrenochrome forms, while when a tartrate buffer

solution with a pH of 6.5 is used, a red-violet colour appears:

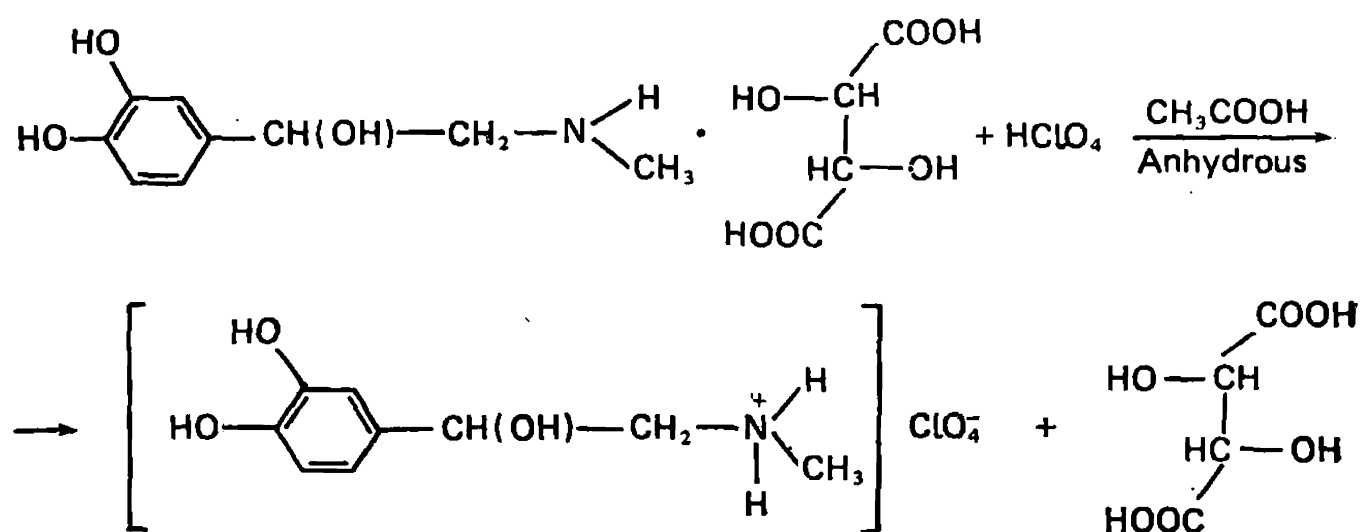


Adrenochrome

This reaction distinguishes adrenaline from noradrenaline, which produces a colour only at a pH of 6.5.

These colour reactions can also be used for the quantitative determination of the drug by photometric methods. For example, the State Pharmacopoeia recommends a photolorimetric method to determine adrenaline hydrogen tartrate in an injection solution in the reaction between the drug and an iron citrate reagent.

The State Pharmacopoeia also recommends the quantitative determination of adrenaline hydrogen tartrate in the crystalline drug by acid-base titration in non-aqueous media; perchloric acid is employed as the titrant, and methyl violet as the indicator:



Since adrenaline is a readily oxidized substance, especially in the presence of an alkali, sodium chloride and also stabilizers, most frequently sodium metabisulphite, are added to its solutions. But even under these conditions, solutions of the drug stored for a long time turn brown, and the physiological activity of the drug drops sharply. The loss of activity is facilitated by alkaline glass of a bottle or ampoules, a high ambient temperature, sunlight, and contact with the air. This is why the drug should be stored in neutral glass

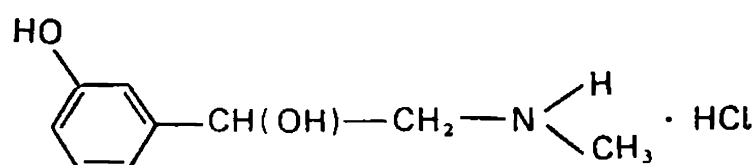
bottles and sealed ampoules filled to the top in a place protected from light. The period up to expiration is one year.

Adrenaline hydrogen tartrate is dispensed in powders, in ampoules containing 1 ml of a 0.18% solution for injections, and in bottles containing 10 ml of a 0.18% solution for external application. Adrenaline is also dispensed in the form of its hydrochloride in 10-ml bottles containing a 0.1% solution for external application and in 1-ml ampoules containing a 0.1% solution for injections. These drugs are not official.

The drug is listed in Group B. Since it can be readily oxidized, adrenaline is an unstable drug and rapidly decomposes. In this connection, investigations were carried out for synthesizing analogues of this drug. Among the multitude of compounds obtained, some of them found use in medicine. A representative of the synthetic analogues of adrenaline is the official drug mesaton (phenylephrine).

Mesaton (*Mesatonum*)

1-(meta-Hydroxyphenyl)-2-methylaminoethanol hydrochloride



$C_9H_{13}NO_2 \cdot HCl$

M.m. 203.67

Mesaton (phenylephrine) differs from adrenaline only in that its molecule is based on monatomic phenol. This substantially increases its stability in comparison with adrenaline. The drug is effective when taken orally and has a more prolonged action.

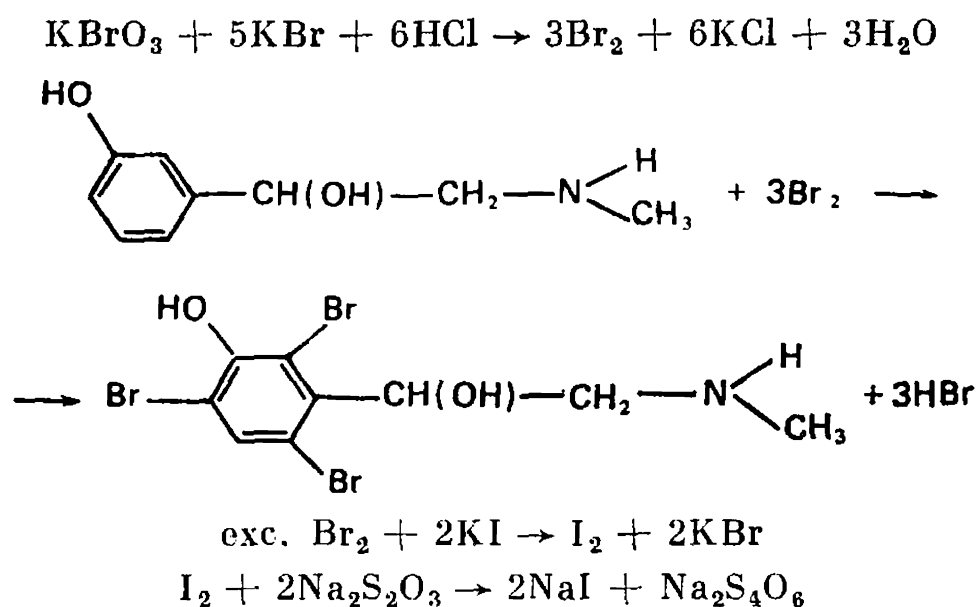
Mesaton is a white crystalline powder, sometimes with a slightly yellowish tint. It dissolves readily in water, alcohol, and dilute solutions of acids and alkalis, and is insoluble in ether. It is identified by:

(a) a reaction with an iron(III) chloride solution (for the phenol hydroxyl group): the solution acquires a violet colour;

(b) a reaction with a copper sulphate solution in the presence of a sodium hydroxide solution: a blue-violet complex forms that does not dissolve in ether (a distinction from ephedrine).

The drug can be determined quantitatively by a number of methods, namely, by neutralization and argentometry (relative to HCl), by titration in non-aqueous media, bromatometry, and photometry.

The State Pharmacopoeia recommends the bromatometric method:



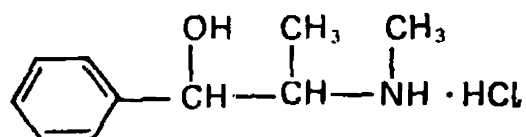
Like adrenaline, mesaton causes constriction of the peripheral blood vessels and accordingly raises the arterial blood pressure. It is dispensed in 0.01-g powders and tablets and in ampoules containing 1 ml of a 1% solution.

It should be stored in well closed orange glass jars; ampoules and tablets should be kept away from the light. The drug is listed in Group B.

The official preparation of ephedrine is ephedrine hydrochloride.

Ephedrine Hydrochloride (*Ephedrini hydrochloridum*)

1-1-Phenyl-2-methylaminopropanol-1-hydrochloride

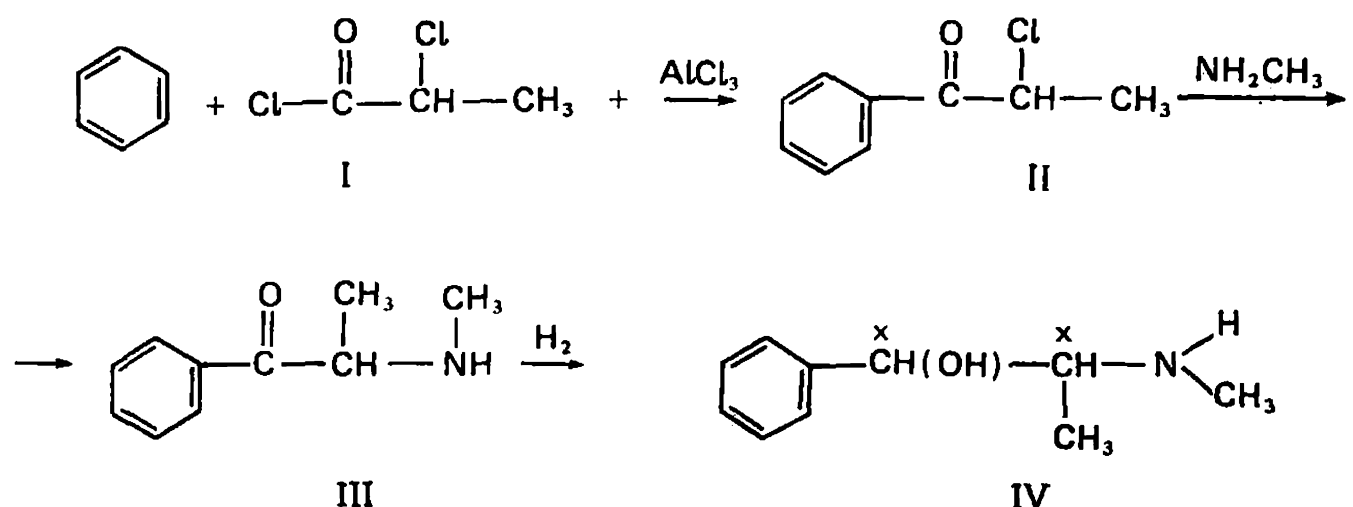


$\text{C}_{10}\text{H}_{15}\text{NO} \cdot \text{HCl}$

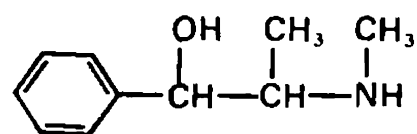
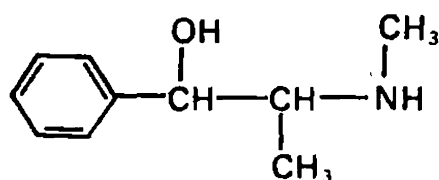
M.m. 201.70

The insignificant content of the natural alkaloid ephedrine in various species of *ephedra* prompted chemists to develop synthetic methods of producing ephedrine. The first complete synthesis of ephedrine and its isomers was carried out by H. Spet (1925). Subsequently, a number of variants of ephedrine synthesis were proposed, but the following one found practical application. The starting substance is benzene, which is condensed with the chloroanhydride of monochloropropionic acid (I) in the presence of aluminium chloride. The obtained chloroethylphenylketone (II) is condensed with

methylamine. The product is a secondary amine (III), which when reduced forms ephedrine (IV):



Ephedrine has two asymmetric carbon atoms, therefore there are four optically active isomers of ephedrine and two racemates. Of the four isomers, the greatest use has been found by ephedrine (*cis*-isomer) and pseudoephedrine (*trans*-isomer), which are space isomers:

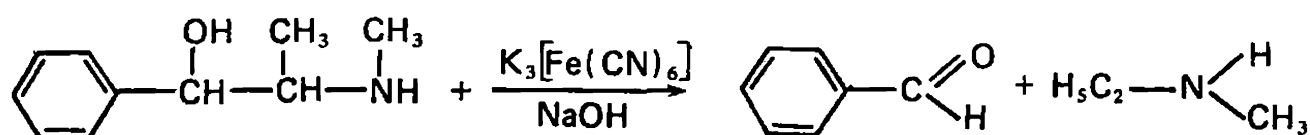
Ephedrine (*cis*-isomer)Pseudoephedrine (*trans*-isomer)

The *cis*-isomer is a levorotatory alkaloid, and the *trans*-isomer is a dextrorotatory one. The recovery of ephedrine from the synthetic product (racemate) is based on the different solubility of the oxalates of the two optical isomers in alcohol. Ephedrine oxalate crystallizes from alcohol in the form of a precipitate, while pseudoephedrine oxalate dissolves in alcohol.

Ephedrine hydrochloride forms colourless acicular crystals or a white crystalline powder without an odour, and with a bitter taste. It dissolves readily in water, is soluble in 95% alcohol, and virtually insoluble in ether. It is identified by:

(a) a reaction with a silver nitrate solution in the presence of nitric acid: a white curdled precipitate of silver chloride forms (Cl^-);

(b) a reaction with potassium ferricyanide in an alkaline medium: a smell of benzaldehyde formed as a result of decomposition of the ephedrine is felt:



(c) a reaction with a copper sulphate solution in the presence of an alkali: a blue colour appears. When ether is added and the vessel with the reaction mixture is agitated and then left standing, the settled ether layer is coloured violet-red, whereas the water layer retains a blue colour.

The preparation must not have an acidic reaction, therefore a tolerated limit of acidity is established. The preparation must contain no organic admixtures.

The content of ephedrine in a preparation can be determined in various ways. The State Pharmacopoeia recommends acid-base titration in non-aqueous media in the presence of mercury(II) acetate. It can be determined photolorimetrically by obtaining a coloured complex with copper sulphate. The method of neutralization and argentometry (for HCl) can be used.

In its physiological action, ephedrine is close to adrenaline. It is chiefly administered in bronchial asthma and a low blood pressure.

Ephedrine is less toxic than adrenaline because it has no phenol hydroxyl groups in its nucleus. For the same reason, it is more stable to oxidation. Salts of ephedrine are active both when taken orally and when injected intramuscularly and intravenously, and do not decompose when boiled.

The drug is dispensed in 0.025-g powders and tablets and in ampoules containing 1 ml of a 5% solution for injections.

It should be stored in well closed jars in a place protected from light. It is listed in Group B.

REVIEW QUESTIONS

1. Which group in a cocaine molecule produces an anaesthetizing effect?
2. What are the shortcomings of cocaine as an anaesthetic?
3. What kind of chemical compound is anesthesin (benzocaine)?
4. Why are the salts of anesthesin unstable and why do they rapidly hydrolyze?
5. Why does anesthesin dissolve poorly in water?
6. What functional group in novocaine (procaine) underlies the reaction of azo dye formation?
7. How can you explain the ability of anesthesin to become brominated?
8. How can you explain the ability of novocaine to decolorize potassium permanganate solutions?
9. Why is it necessary to extract the novocaine base with chloroform if novocaine is determined quantitatively by neutralization?
10. Why is novocaine injected together with penicillin?
11. Why is dicaine (tetracaine) hydrochloride first hydrolyzed when it is determined quantitatively by nitritometry?
12. If dicaine is determined quantitatively by neutralization, chloroform is added. Why?
13. Compare the pharmacological properties of novocaine and dicaine.

14. Write the equations of the reactions for the quantitative determination of PAS-Na by nitritometry, neutralization, bromatometry, and iodochlorometry.

15. What underlies the mechanism of the pharmacological action of bepask (calcium benzamidosalicylate)?

PRACTICAL LESSON

Analysis of Novocaine (Procaine)

1. Perform identification reactions:

(a) dissolve 0.5 g of the drug in 1 ml of water. Add five drops of a 2 *N* nitric acid solution and five drops of a silver nitrate solution. Pour a part of the test tube contents into another tube and add an ammonium hydroxide solution;

(b) dissolve 0.05 g of the drug in 3 ml of water, add six drops of sodium hydroxide, and agitate the mixture well;

(c) dissolve 0.05 g of the drug in 1 ml of water, add three drops of a 2 *N* hydrochloric acid solution, three drops of a sodium nitrite solution, and shake the mixture. Add several drops of this solution to 1 ml of an alkaline solution of 2-naphthene;

(d) dissolve 0.05 g of the drug in 2 ml of water, add three drops of a 2 *N* sulphuric acid solution and three drops of a potassium permanganate solution.

Write your observations in your notebook. Write the equations of the chemical reactions.

2. Conduct a quantitative determination by two methods:

(a) transfer 0.1 g of the drug into a conical flask through a funnel, dissolve the sample in 10 ml of water and 10 ml of hydrochloric acid, add through the funnel 0.3 g of potassium bromide, and wash it into the flask with 6 ml of water. Add eight drops of tropeolin-00 and one drop of methylene blue as indicators. Slowly titrate with a sodium nitrite solution until the colour changes from red-violet to light blue.

Write the equation of the chemical reaction. Name the method used for the quantitative determination. Perform calculations and make a conclusion on the results of the analysis;

(b) transfer 0.1 g of the drug into a conical flask through a funnel, wash the funnel with 5 ml of alcohol, and shake the mixture to dissolve the novocaine, add five drops of a phenolphthalein indicator, and titrate with a 0.1 *N* sodium hydroxide solution until a pink colour appears.

Name the method used for the quantitative determination. Write the equation of the chemical reaction. Perform the relevant calculations.

Compare the results obtained and conclude on the merits and shortcomings of the two methods. Which method do you recommend for the quantitative determination of novocaine?

Chapter 25. Organo-Elemental Compounds

Compounds in whose molecule carbon is bound directly to a metal or non-metal, e.g. $R-C-Me-C-R'$, are called **organo-elemental compounds**. These compounds are widely employed in various branches of the national economy such as the chemistry of polymers, in engi-

neering, and agriculture. They are also used in medicine because many of these compounds exhibit a physiological activity.

Compounds of mercury were among the first organo-elemental ones introduced into medicine. Next the physiological activity of arsenic compounds was discovered. They are highly effective in the treatment of diseases such as syphilis and recurrent typhoid fever. At that time, there were no other means of treating these diseases.

The creation and development of chemotherapeutic agents and, in particular, of organic arsenic compounds are associated with the name of the German chemist and biologist P. Ehrlich (1854-1915). He advanced the idea of obtaining chemical substances that would act selectively on microbes and at the same time would not harm the macroorganism. This is the essence of chemotherapeutics.

In conducting his research in the field of organic arsenic compounds, Ehrlich prepared an enormous number of diverse arsenic compounds, but only preparation No. 606, which he named salvarsan, produced the desired physiological effect. This substance selectively acted on microbes without harming a macroorganism. Later his preparation No. 914 was found to be still more valuable. Ehrlich called it neosalvarsan.

By developing salvarsan and neosalvarsan, Ehrlich opened up the possibility for the further search for chemotherapeutic agents. The search for chemotherapeutic medicaments from the group of organo-elemental compounds received great impetus in the USSR in the last few decades. The Soviet scientists I. Ostromyslensky, N. Kizhner, G. Kirchhoff, and M. Kraft worked in this field. The centre of these investigations was the USSR Chemico-Pharmacological Research Institute, where many valuable drugs were synthesized including novarsenol (neoarsphenamine), myarsenol (sulpharsphenamine), osarsol (acetarsol), and aminarsone (carbarsone). To date, the organic compounds of arsenic and mercury have retained their significance.

25.1. ORGANIC COMPOUNDS OF ARSENIC

The organic arsenic compounds of the aliphatic series, although some of them (sodium cacodylate, arrhenal) exhibit physiological activity, have not taken root in medicine because of their high toxicity. Further studies were directed at searching for physiologically active aromatic compounds of arsenic where it exhibits an oxidation state of three and five.

Of the compounds of this series, osarsol, aminarsone, salvarsan, novarsenol, and myarsenol have found application in medicine.

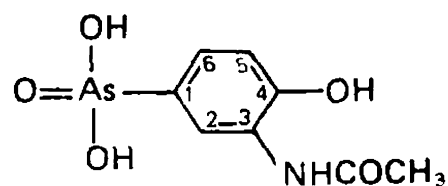
The arsenic in these compounds is bound directly to carbon and is not ionogenic, consequently, it cannot be determined by conventional analytical reactions of the ionic type.

In this connection, the methods of analysing organo-elemental compounds have their features. To detect an element in an organic molecule, in the given case arsenic, it has to be transformed into an ionogenic state. This is achieved in two ways, namely, (a) by sintering the preparation with a mixture of $\text{Na}_2\text{CO}_3 + \text{NaNO}_3$ to transform the arsenic to sodium arsenate Na_2HAsO_4 ; and (b) by heating the preparation with a mixture of sulphuric and nitric acids or a mixture of potassium permanganate with sulphuric acid to form arsenic acid H_3AsO_4 . In both cases, the arsenic is detected by one of the reactions characteristic of As^{5+} , for example, with a magnesia mixture.

Representatives of organic arsenic compounds in which the arsenic is in the oxidation state of five that have found application in medicine are osarsol and aminarsone. These drugs are pharmacopoeial ones.

Osarsol (*Osarsolum*)

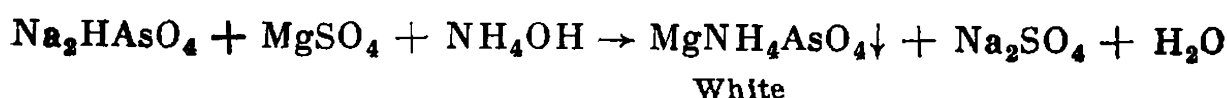
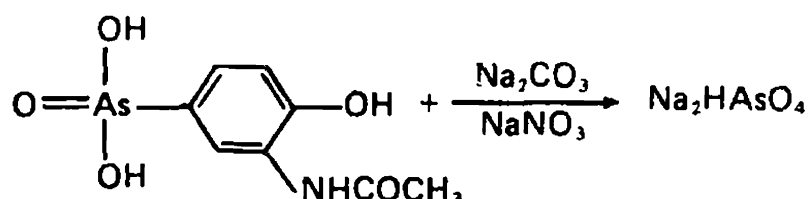
3-Acetamino-4-phenolarsonic acid



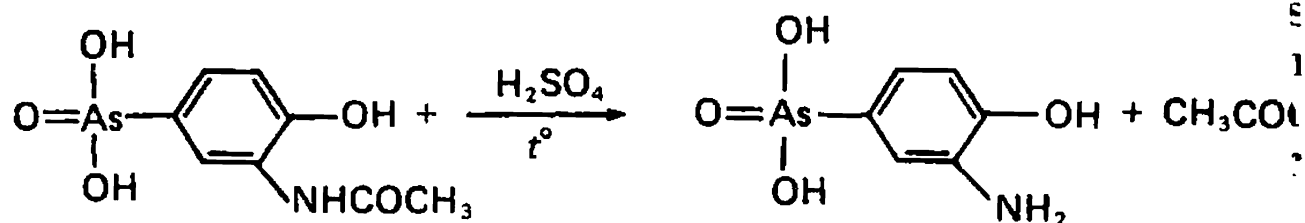
M.m. 275.09

Osarsol (acetarsol, acetphenarsine) is a white odourless crystalline powder. It has acidic properties and dissolves in a carbonate solution (owing to the hydroxyls of the arsonic acid residue) and in an alkali solution (owing to the phenol hydroxyl and the arsonic acid residue). The drug dissolves very sparingly in water and alcohol. It is identified by:

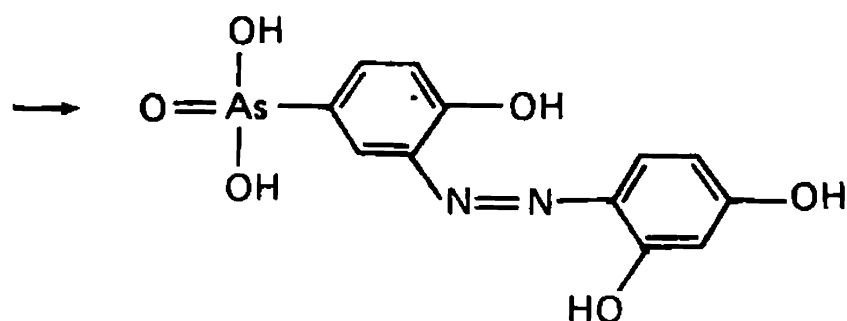
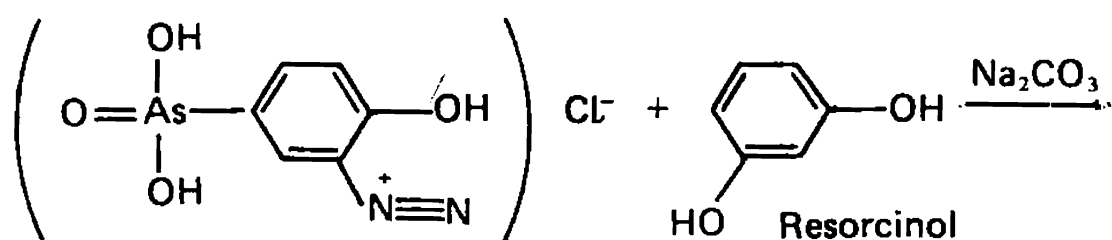
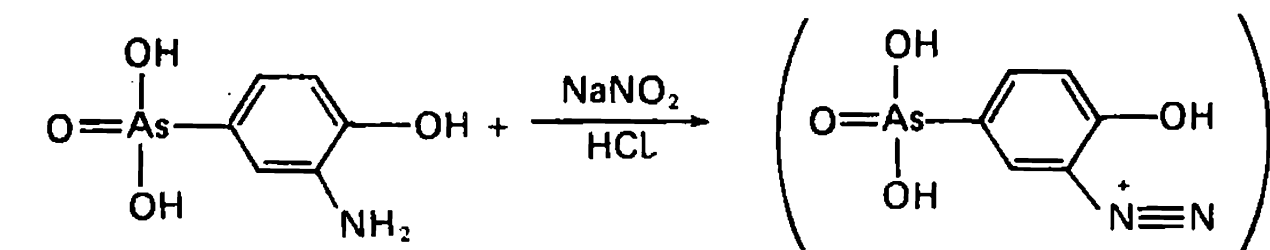
(a) the formation of a white crystalline precipitate after sintering the drug with a sintering mixture and adding the magnesia mixture $\text{MgSO}_4 + \text{NH}_4\text{Cl} + \text{NH}_4\text{OH}$:



(b) the smell of acetic acid formed after boiling the drug with dilute sulphuric acid (hydrolysis):



(c) the formation of an azo dye of 3-amino-4-hydroxybenzoic acid as a result of hydrolysis of the drug:



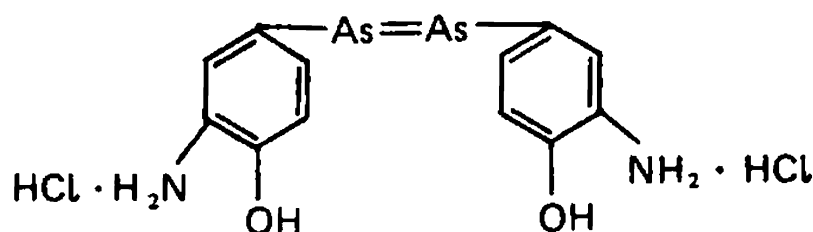
Red azo dye

To determine the quality of the drug, the State Pharmacopoeia requires it to be tested for admixtures of inorganic arsenic compounds (arsenates), because they are more poisonous, and for free amines.

The State Pharmacopoeia recommends determining the amount of osarsol in the drug by bromatometry after transforming the covalently bound arsenic into the ionogenic state. For this purpose, a sample of the drug is heated with a mixture of nitric and sulphuric acids. The product is arsenic acid which is reduced with hydrochloric acid and sulphate to arsenic oxide. The latter is determined bromatometrically.

Osarsol is employed in the treatment of syphilis, recurrent fever, and dysentery. If the urine contains protein, its use is prohibited.

spensed in 0.25-g powders and tablets. It is listed in Group
entatives of arsenic aromatic compounds in which the ar-
an oxidation state of three are drugs of the salvarsan series—
ol (neoarsphenamine) and myarsenol (sulpharsphenamine).
ugs are derivatives of salvarsan:



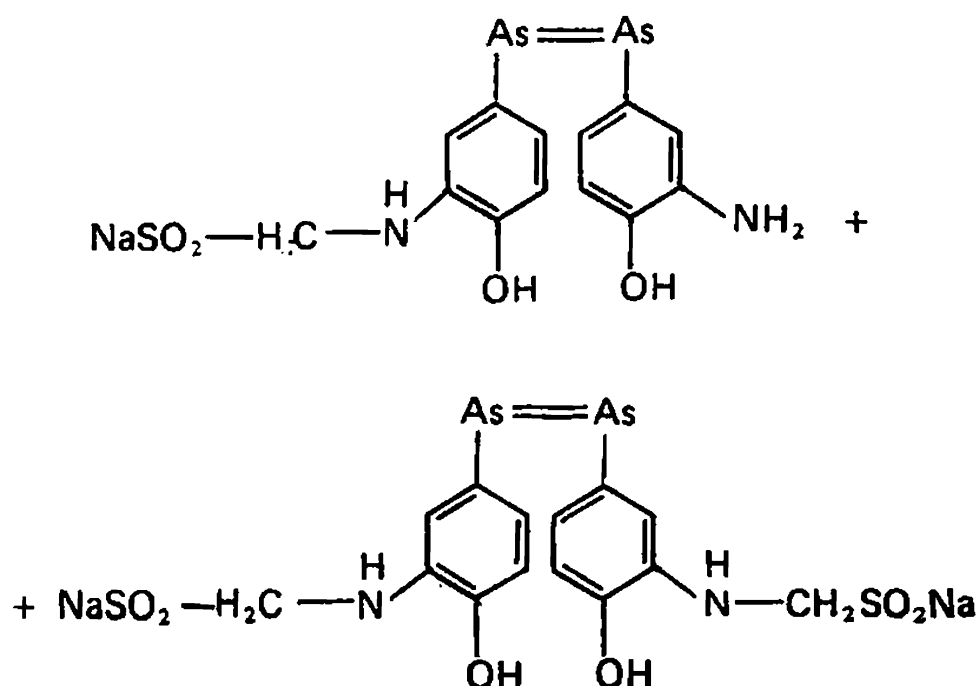
Salvarsan

first synthesized, it played an enormous role in the chemo-
of a number of infectious diseases. However, its use was re-
by a number of shortcomings, which triggered off a search
e improved and better drugs.

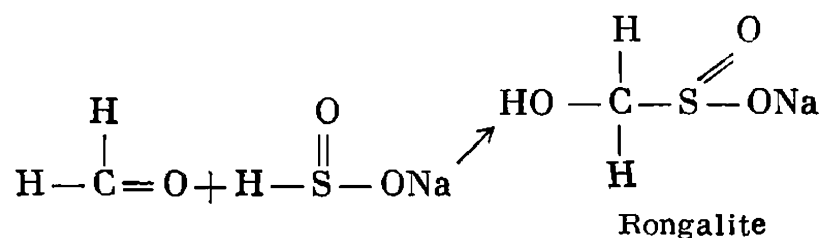
USSR, a drug of the type of Ehrlich's neosalvarsan was syn-
. It was named novarsenol. It is a mixture of mono- and
tuted compounds of salvarsan with rongalite.

Novarsenol (*Novarsenolum*)

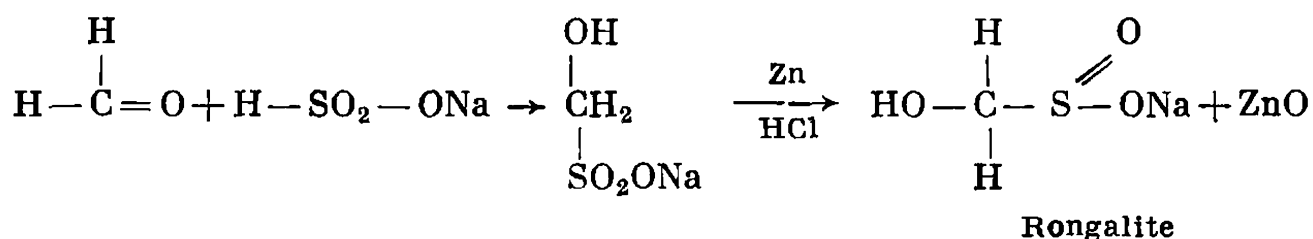
ture of sodium 3,3'-diamino-4,4'-dihydroxyarsenobenzene-*N*-
hydresulphoxylate and sodium 3,3'-diamino-4,4'-dihydro-
benzene-*N,N'*-bis-formaldehydesulphoxylate



Rongalite (sodium formaldehyde sulphonylate) is a compound of formaldehyde with sodium hydrogen sulphonylate:



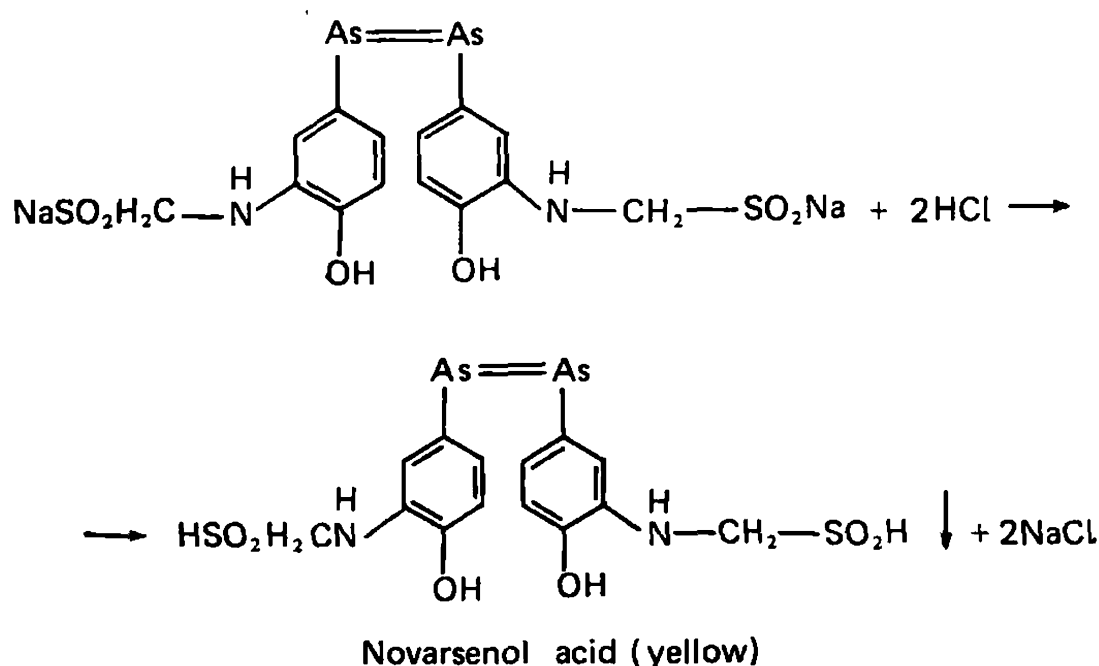
It is produced by condensing formaldehyde with sodium hydrogen sulphite with the subsequent boiling of the solution with zinc dust in the presence of an acid:



Novarsenol is a yellow powder readily soluble in water. Its yellow aqueous solution has a neutral or weakly alkaline reaction. It is practically insoluble in absolute alcohol and ether. The drug is identified by:

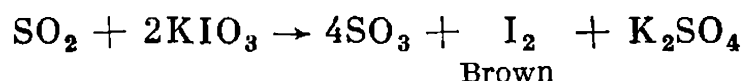
(a) the formation of a white crystalline precipitate after sintering the drug with a sintering mixture and the subsequent addition of a magnesia mixture (organically bound arsenic);

(b) the formation of a yellow precipitate of novarsenol acid after acidification of the drug with dilute hydrochloric acid:



(c) the evolution of sulphur dioxide when the drug has been heated with mineral acids (decomposition of the rongalite); the sulphur di-

oxide is detected by the blue colour of a piece of filter paper wetted with a potassium iodate and starch solution:



(d) the decoloration of indigo carmine (a distinction from myarsenol); the indigo carmine loses its colour because it is oxidized by the rongalite in whose molecule the S^{4+} is reduced to S.

The content of novarsenol in the drug is determined by bromatometry after heating the drug with a mixture of nitric and sulphuric acids (see the quantitative determination of arsenous anhydride, p. 97).

Novarsenol is administered in the same cases as osarsol. It is introduced intravenously.

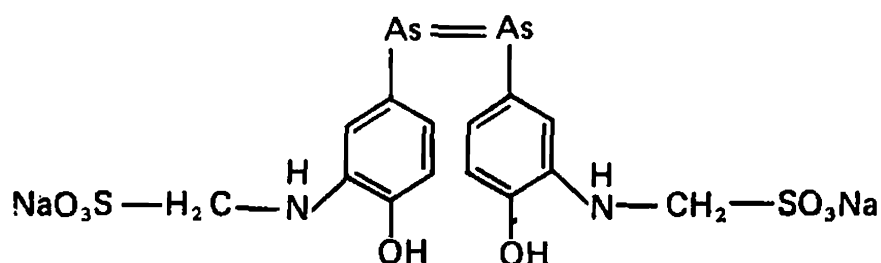
The drug is dispensed in a powder in sealed ampoules containing 0.15, 0.3, 0.45, or 0.6 g.

A solution for injections is prepared with sterile water. The ampoules should be stored in a cool place protected from light. The drug is listed in Group A.

Novarsenol contains S^{4+} in its molecule. It is therefore unstable and is readily reduced. To eliminate this shortcoming, the drug myarsenol was synthesized. It is the condensation product of salvarsan with sodium hydroxymethylenesulphonate.

Myarsenol (*Myarsenolum*)

Sodium 3,3'-diamino-4,4'-dihydroxyarsenobenzene-N,N'-bis-methanesulphonate



$\text{C}_{14}\text{H}_{14}\text{As}_2\text{N}_2\text{Na}_2\text{O}_8\text{S}_2$

M.m. 598.22

Myarsenol (sulpharsphenamine, thioarsphenamine) is a pale yellow light amorphous powder. It dissolves readily in water and is practically insoluble in alcohol and ether. The drug is identified by:

(a) a reaction for As^{3+} after heating the drug with a mixture for sintering (see the reactions for the identification of arsenous anhydride, p. 96);

(b) a reaction with a silver nitrate solution; a brown colour appears (the reducing ability of the phenol hydroxyl groups).

Myarsenol does not decolour an indigo carmine solution because it contains S^{6+} in its molecule.

The content of myarsenol in the drug is determined like that of novarsenol by bromatometry after transferring the organically bound arsenic into an ionogenic state.

Myarsenol, unlike novarsenol, may be introduced intramuscularly. This explains the name of the drug.

The drug is dispensed in the form of a powder sealed in ampoules. Its administration and conditions of storage are the same as for novarsenol. It is listed in Group A.

REVIEW QUESTIONS

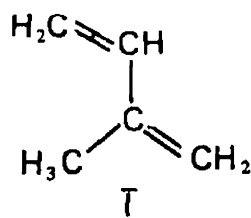
1. What compounds are called organo-elemental ones?
2. Why does osarsol dissolve in alkalis and carbonates?
3. Why does osarsol have to be boiled with an acid before diazotizing is commenced?
4. Why is arsenic in organo-elemental compounds detected only after mineralization?
5. What explains the lower toxicity of myarsenol in comparison with novarsenol?

Chapter 26. Terpenes

Terpenes are an important class of organic compounds found in both animals and plants. In the latter, they are contained in many essential oils. But essential oils and resins together with terpenes contain other compounds that are derivatives of terpenes with various functional groups.

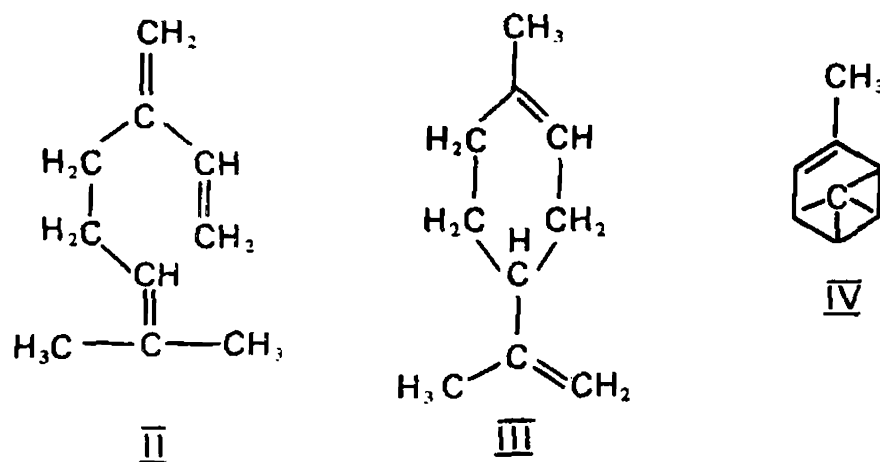
D. Mendeleev was among the first Russian scientists to study essential oils and resins. The outstanding organic chemist A. Butlerov gave much attention to studying essential oils. His doctor's thesis was devoted to this problem. A major contribution to the chemistry of terpenes was made by professor E. Wagner of the Warsaw University, and the Russian and Soviet scientists L. Flavitsky, L. Chugayev, S. Nametkin, G. Pigulevsky, A. Arbuzov, and others.

The carbon skeletons of the terpenes consist of repeating structural units of the five-carbon compound isoprene C_5H_8 (I):



Terpenes with two isoprene units $(C_5H_8)_2$, i.e. $C_{10}H_{16}$, are called **monoterpenes**, those with four units $(C_5H_8)_4$ are **diterpenes**, with six units $(C_5H_8)_6$ are **triterpenes**, with eight units $(C_5H_8)_8$ are **tetraterpenes**, and so on. Terpenes with three isoprene units $(C_5H_8)_3$ are called **sesquiterpenes**.

Monoterpenes are used in medicine. They are divided, in turn, into three groups, namely, (1) acyclic (with an open chain) with three double bonds (II); (2) monocyclic with two double bonds in the molecule (III); and (3) dicyclic (with one double bond) (IV):



The formulas of the terpenes show that they are hydroaromatic (alicyclic) compounds.

Terpenes with an open chain have not found any application in medicine, while the cyclic monoterpenes include widely known drugs such as menthol, terpin hydrate (monocyclic terpenes), and camphor (a dicyclic terpene).

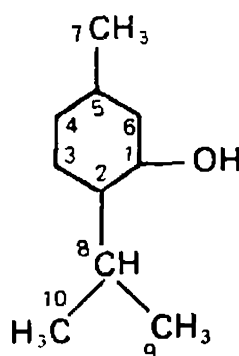
The medicinal use of terpenes is based on their antiseptic and disinfecting properties. Some terpenes are used as expectorants (terpin hydrate), and as stimulators of cardiac activity and respiration (camphor).

26.1. MONOCYCLIC TERPENES

Menthol and terpin hydrate are pharmacopoeial drugs of the monoterpene series.

Menthol (*Mentholum*)

l-2-Isopropyl-5-methylcyclohexanol

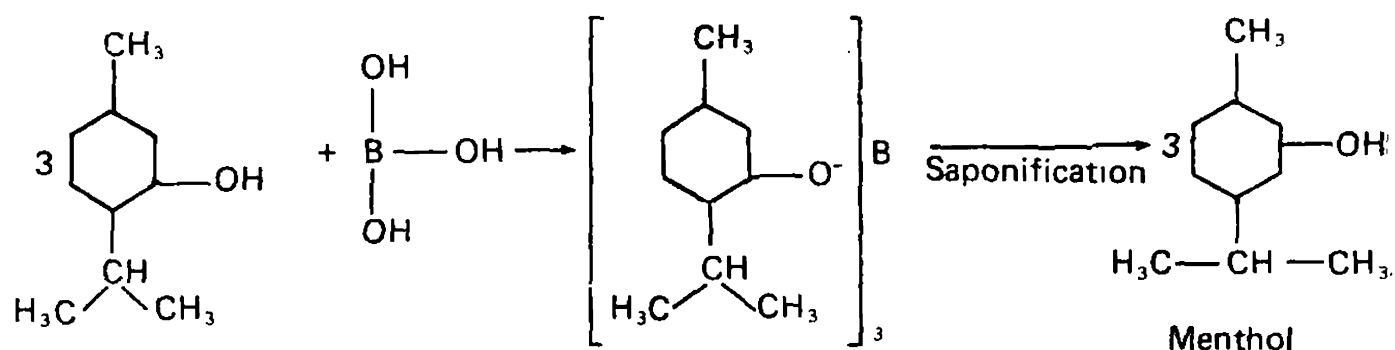


$C_{10}H_{20}O$

M.m. 156.27

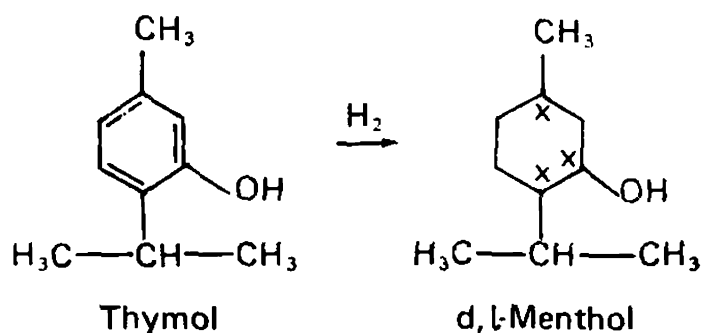
Menthol is contained in oil of peppermint together with an acetic acid ester. It is produced from this essential oil by the borate method or by freezing out if its content in the essential oil is at least 80%.

The borate method developed by B. Rutovsky is intended for grades of essential oil containing 50-60% of menthol. The oil of peppermint is heated with boric anhydride or boric acid under a reduced pressure. The formed boric ether of menthol has a very high boiling point and is therefore easily separated from the other components of the essential oil. The boric ether is distilled with steam, and already in the process of distillation the ether becomes saponified and menthol separates immediately:



The freezing out method consists in the following: the oil of peppermint is distilled and the fraction boiling within the limits of 208-212 °C, which contains chiefly menthol, is frozen out with the aid of a special cooling mixture. Next it is centrifuged or filtered. After recrystallization, pure crystalline menthol is obtained.

In the most widespread synthetic method, menthol is produced from thymol by hydrogenation in the presence of catalysts (nickel, platinum, etc.):



This method yields crystalline menthol in the form of the optically inactive d,l-menthol.

Menthol is an optically active substance. It has eight optically active isomers and four racemates, which is due to the three asymmetric carbon atoms in its molecule (C₁, C₃, and C₄).

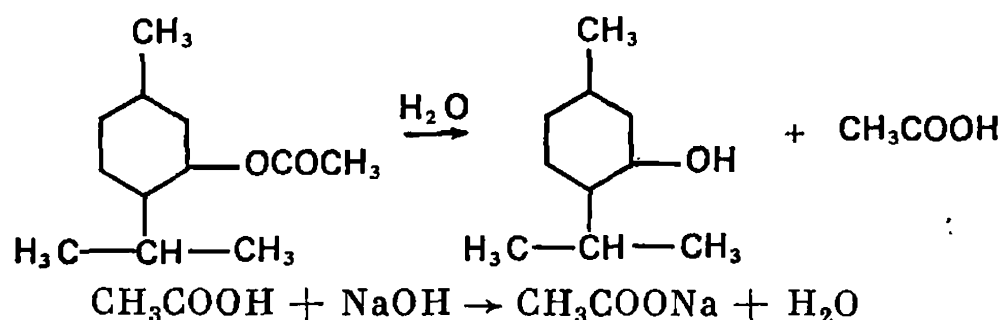
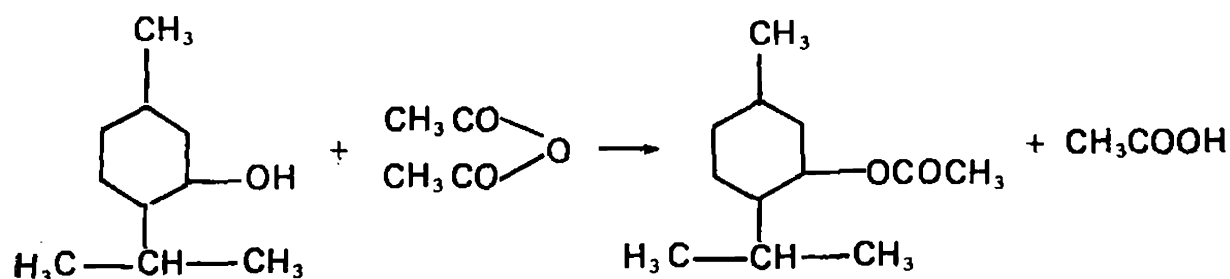
Menthol forms colourless crystals with a strong peppermint odour and a cooling taste. It dissolves poorly in water, readily in 95% alcohol, ether, and acetic acid. From the chemical viewpoint, menthol is a secondary alcohol because its oxidation yields a ketone (menthone).

Menthol is mainly identified by its physical properties, namely, its melting point (41-44 °C) and its specific rotation (from 49 to

51° for a 10% solution in 95% alcohol). These properties are also a criterion of the purity of the preparation.

Of the chemical identification reactions, the official one is that with a 1% solution of vanillin in the presence of concentrated sulphuric acid; a yellow colour appears that becomes crimson when a small amount of water is added.

The content of menthol in a preparation is determined by acetylation. Menthol acetate is obtained, which is then subjected to saponification. The formed acetic acid is titrated with an alkali (NaOH) to achieve a phenolphthalein end point:

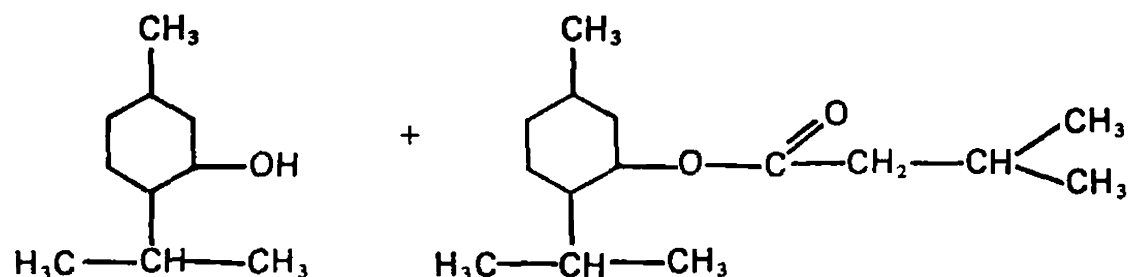


Menthol is employed as an antiseptic in inflammation of the mucous membranes of the nose and throat (ephedrine with menthol in the form of nose drops). It is used together with oil of peppermint in tooth powder and paste, and for gargling and irrigation. Menthol also exhibits a light local anaesthetic action, therefore it is included in the composition of some tranquilizers for treating neuralgic and rheumatic pains.

Of the menthol esters, validol is used as a drug.

Validol (*Validolum*)

Solution of menthol in menthyl isovalerate



$\text{C}_{10}\text{H}_{20}\text{O}$
 $\text{C}_{15}\text{H}_{28}\text{O}_2$

M.m. 156.27
M.m. 240.39

Validol is a transparent, colourless, oily liquid with the odour of menthol. It dissolves readily in alcohol and is insoluble in water. When reacted with vanillin in concentrated sulphuric acid, a crimson colour appears (menthol). The specific gravity of validol is 0.894-0.907.

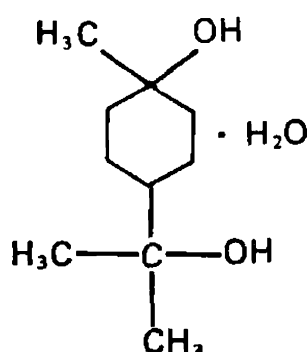
The drug is determined quantitatively by saponification of the ester group: validol is heated with an alcohol solution of an alkali whose excess is titrated with hydrochloric acid.

It is administered as a spasmolytic (vasodilating) agent in angina pectoris and neuroses.

It is dispensed in the form of tablets and a liquid. The latter is prescribed in drops (to be used on sugar). A 5-10% alcohol solution is employed for treating skin itch. The drug should be stored in a cool place in well closed jars.

Terpin Hydrate (*Terpinum hydratum*)

para-Menthane-1,8-diol



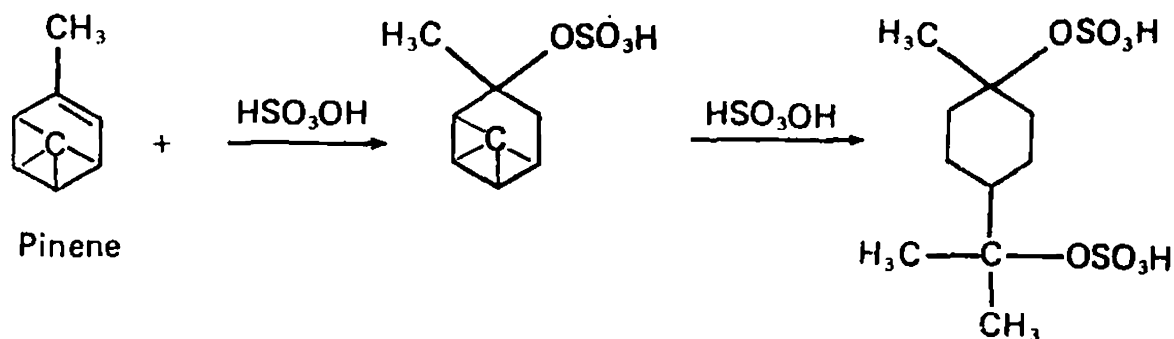
$C_{10}H_{20}O_2 \cdot H_2O$

M.m. 190.28

Terpin hydrate differs in its structure from menthol in that it is a ditertiary alcohol derivative of menthane.

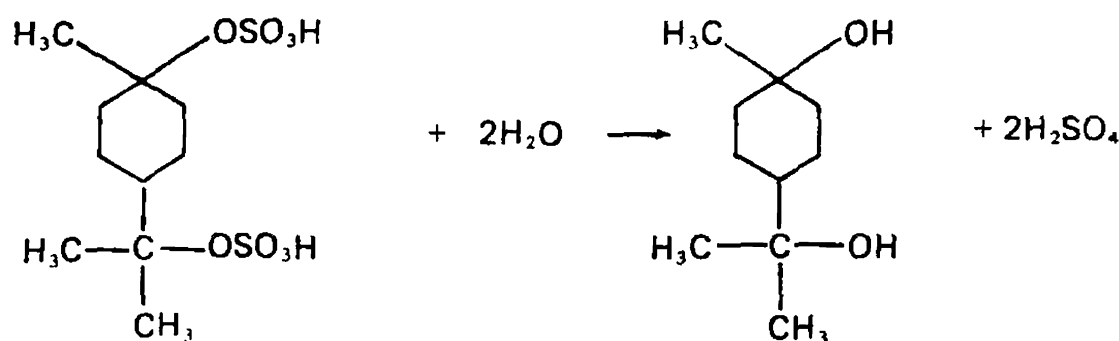
Terpin hydrate is produced by the hydration of pinene—the main constituent of turpentine oil. Sulphuric acid is the hydrating agent and catalyst of the hydrating process. This method is a commercial one.

Pinene is hydrated in the presence of sulphuric acid via an intermediate—sulphuric acid ester:



The formed ester is unstable and is readily saponified to sulphuric

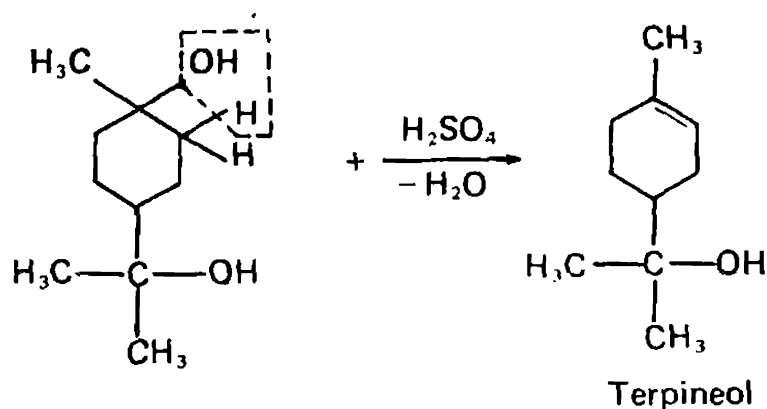
acid and a ditertiary alcohol—terpin hydrate:



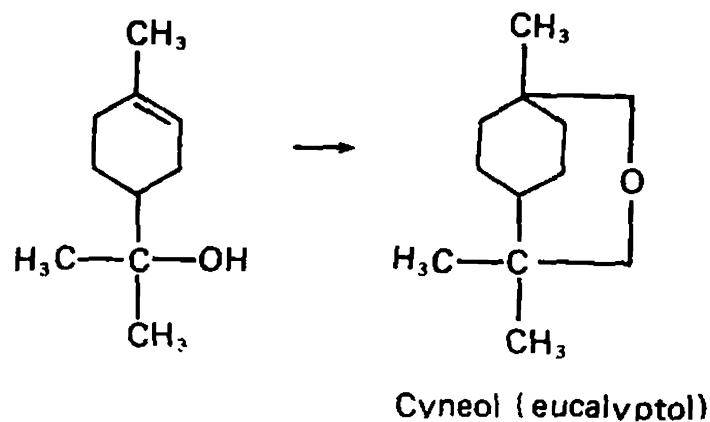
Terpin hydrate forms colourless transparent crystals or a white crystalline powder without an odour and with a slightly bitter taste. It dissolves only slightly in water, chloroform, ether, and turpentine. It dissolves with difficulty in boiling water, is soluble in 95% alcohol and still better in boiling alcohol. When carefully heated to 100°C , terpin hydrate sublimes to form acicular crystals. Terpin hydrate solutions have a neutral reaction to litmus.

The following reactions are used to identify terpin hydrate:

(a) dehydration in the presence of sulphuric acid; the product is the unsaturated alcohol terpineol with an aromatic odour (official reaction):



With an excess of the sulphuric acid, the reaction can proceed further with the formation of cineol or eucalyptol, a camphor odour being felt (cineol is contained in many essential oils, especially of eucalyptum and santonica):



(b) when a 3% alcohol solution of iron(III) chloride is added to the

drug and then evaporated, carmine, violet, and green tints appear. When benzene is added, the latter turns blue (official reaction).

Since terpin hydrate is a tertiary alcohol, it cannot be oxidized by iron(III) chloride and other oxidizing agents; it can be assumed that the tints are due to the decomposition products of terpin hydrate. The benzene extracts these products and acquires a blue colour.

To determine the purity of the drug, its physicochemical indices are determined: terpin hydrate should evaporate without an odour. It should also have a neutral reaction to litmus.

There are two official preparations of terpin hydrate: a powder and tablets—*Tabulettæ Terpini hydrati 0.25 aut 0.5*.

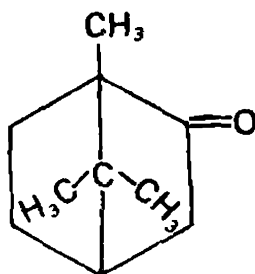
No quantitative determination is required by the State Pharmacopoeia for the powder, while the gravimetric method is recommended for the tablets. By this method, a sample of ground tablets is agitated with 95% ethanol, and the suspension is filtered. A definite amount of the filtrate is transferred to a weighing bottle. The alcohol is evaporated in a water bath, and the residue is dried up to a constant mass and weighed.

The drug is administered in chronic bronchitis as an expectorant in a daily dose of 0.2-0.5 g, and sometimes in oedemae as a uretic. Large doses are toxic and irritate the kidneys.

It is dispensed in powders and tablets in combination with codeine and soda. It should be stored in well closed jars in a cool place.

26.2. DICYCLIC TERPENES

Camphor (*Camphora*)



$C_{10}H_{16}O$

M.m. 152.24

The main natural sources of camphor are the essential oils of the camphor tree (*Cinnamomum camphora*) and the hoary basil (*Ocimum canum*), which contain camphor.

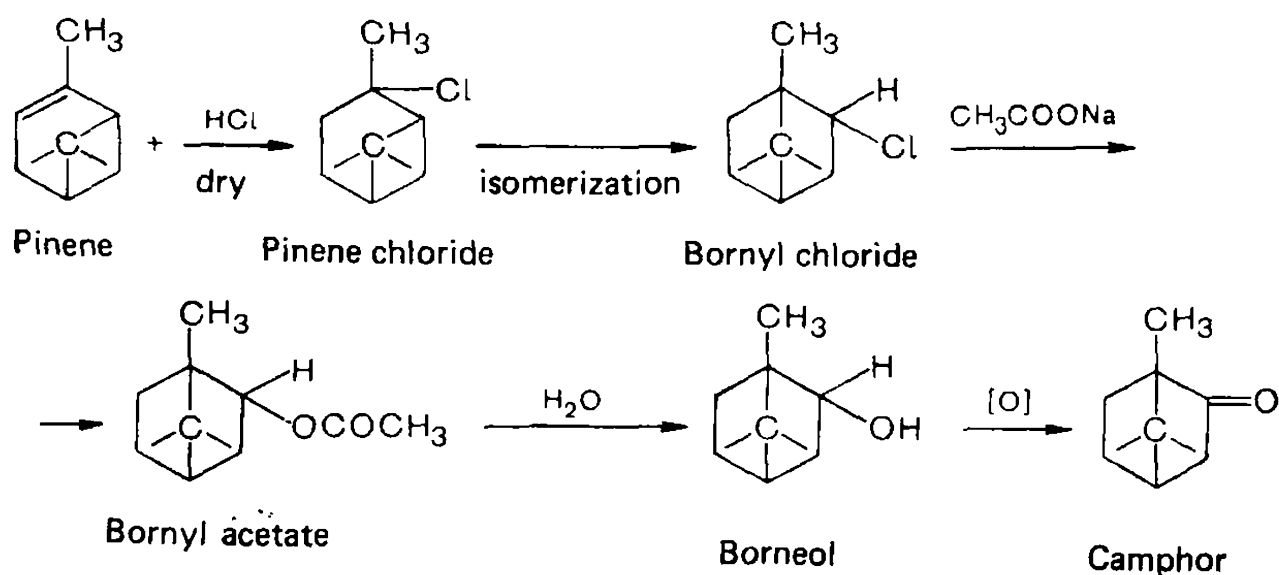
The camphor tree grows in many tropical and subtropical countries and forms forests, which were especially numerous in Japan and China. Attempts were made to cultivate the camphor tree in Russia (at the end of the 19th century) on the Black Sea coast of the Caucasus, but the climatic conditions were unfavourable for it.

The camphor tree is a giant one, sometimes reaching a height of 50 m and a diameter of 5 m. Such a tree was discovered in China; its age was 1400 years. But such ancient trees have been felled long ago and this is why younger plantations which have been growing 40 years or more began to be used.

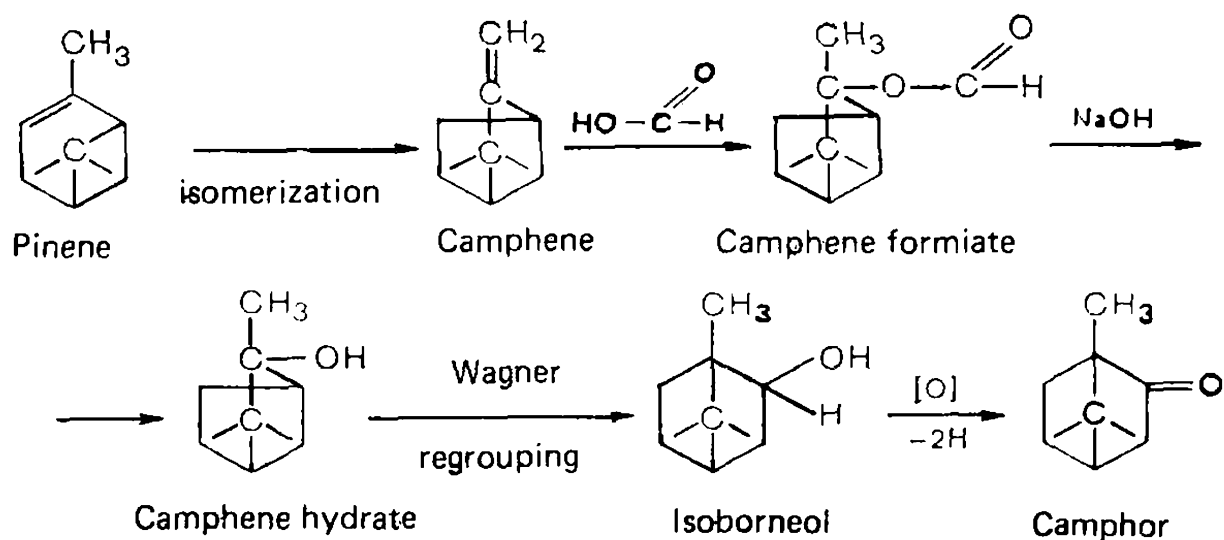
The camphor yield depends on the species of the camphor tree, its age, and on what parts of the tree are used for this purpose. The yield increases with the age of a tree. Generally the camphor tree is used for the production of camphor at an age of 80-100 years.

For a long time, Japan was the chief supplier of camphor, but the high cost of the imported substance and the monopolistic position of Japan on the world market made other countries, including Russia, find ways of producing it synthetically. Almost all the variants of synthesizing camphor use pinene contained in turpentine oil, and also in the oils of sage, juniper, eucalyptus, and peppermint, as the starting substance.

The first synthesis of camphor via bornyl chloride, which is called the bornyl-chloride method, was for a long time the only industrial method of producing camphor. It can be depicted schematically as follows:



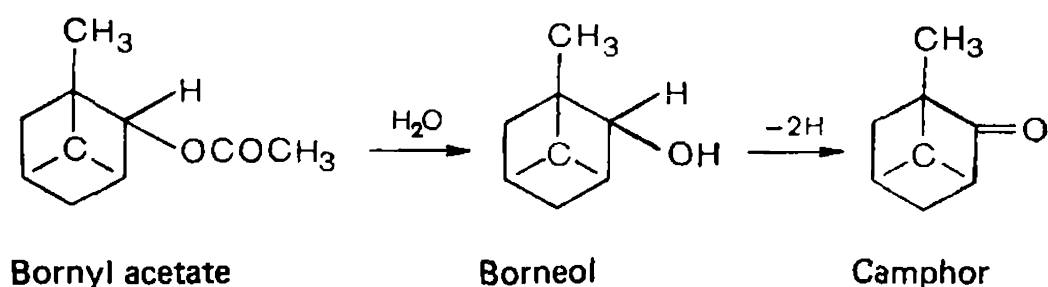
Later a simpler and cheaper variant of this method was developed. It was called the isomerization method of camphor synthesis. Pinene by isomerization according to V. Tishchenko's method was transformed into camphene, and the latter was transformed into camphor:



This method is a commercial one. It is used by most enterprises in the world.

The camphor produced synthetically is racemic.

It was later found that the essential oil of the fir tree is a still more valuable raw material for the production of camphor. This oil contains as its main product bornyl acetate, whose saponification yields borneol. Catalytic dehydrogenation of the latter yields camphor:



Thus, a number of stages are eliminated when oil of fir is used, which substantially cuts the cost of camphor production.

Fir shoots are the raw material used to produce oil of fir. They are distilled with steam to separate the oil. The latter is a greenish-yellow transparent liquid with an aromatic odour of conifer needles. The composition of the oil is not uniform chemically, therefore it is subjected to fractional distillation. The fraction boiling above 180 °C contains bornyl acetate, which is just what is employed to produce camphor.

The first semisynthetic method of producing camphor from oil of fir was embodied by the Russian scientist P. Golubev. The synthesis of camphor from fir shoots was first carried out in 1907, but it was not developed in prerevolutionary Russia owing to the drop in the prices of Japanese camphor. And only after the October Revolution, beginning from 1929, the first production of camphor from fir shoots was inaugurated in the USSR at the Okhtinsk Chemical Works in Leningrad.

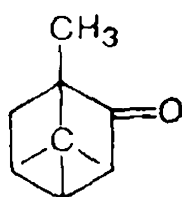
The camphor produced from the oil of fir differs in its physicochemical properties from the Japanese camphor only in that it is levorotatory, but in its physiological action it is in no way inferior to the natural dextrorotatory Japanese camphor.

The State Pharmacopoeia tolerates the use of the d- and l-isomers of camphor in medicine, but the racemic camphor produced synthetically may be employed only externally owing to its low degree of purity.

Camphor is composed of white crystalline lumps or a colourless crystalline powder with a pungent typical smell and a spicy bitter and cooling taste. Camphor crystals readily cake into solid lumps, while under a slight pressure they transform into a transparent block. Camphor is volatile, easily sublimes, and can be distilled

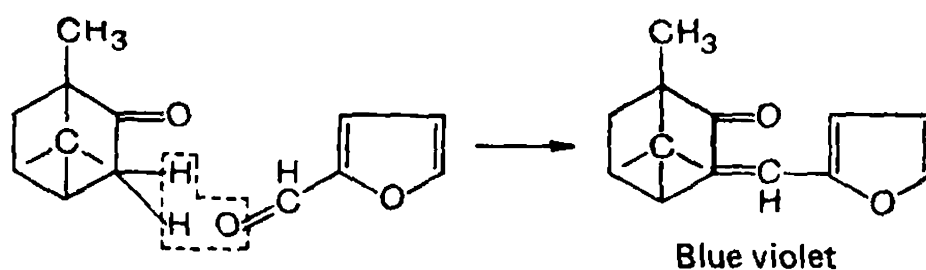
with steam. It dissolves only slightly in water and readily in ethanol, ether, chloroform, fatty and essential oils. It is difficult to grind camphor into a powder because of its viscosity. To facilitate this, it is wetted with a small amount of ether or alcohol.

When ground with phenol, menthol, thymol, or chloral hydrate, camphor forms thick transparent liquids (eutectic mixtures). A camphor molecule contains two asymmetric carbon atoms, but instead of four, only two optical isomers of camphor and one racemic form are known; the latter is shown below:



The main functional group in a camphor molecule determining its identification reactions is the keto group (the formation of oximes, phenylhydrazones with a definite melting point; see Chap. 13).

Camphor has a mobile hydrogen atom adjacent to the keto group and can therefore enter into a condensation reaction with aldehydes. The condensation products are often coloured, and consequently this reaction can be used to identify camphor. For example, when condensed (in the presence of sulphuric acid as a water-removing agent) with furfural, a blue-violet colour appears:



Similarly, a red colour appears in a reaction with formaldehyde. These colour reactions can also be used for the quantitative determination of camphor by photocolorimetry.

A typical constant of camphor is its specific rotation, which varies from $+41$ to $+44^\circ$ for dextrorotatory camphor, and for levorotatory camphor, from -39 to -44° (a 10% solution in 95% alcohol).

The State Pharmacopoeia stipulates that camphor must meet the following requirements:

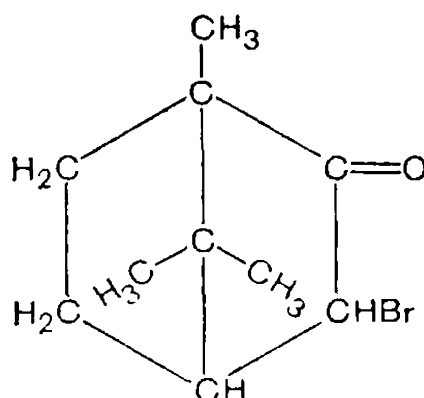
- (1) when 1 g of camphor is dissolved in 4 ml of alcohol, the solution must be transparent and colourless;
- (2) when 1 g of the drug is dissolved in 10 ml of petroleum ether, there should be no turbidity (water);
- (3) when the drug is pressed between sheets of white writing paper, no grease spots should appear.

The State Pharmacopoeia does not require the quantitative determination of camphor in the dry drug, but it is recommended to determine the content of camphor in an oil solution of camphor for injections (*Solutio Camphorae oleosa 20% pro injectionibus*) by the gravimetric method.

Camphor is administered as a cardiotonic in deterioration of cardiac activity and as a stimulator of the central nervous system. Sometimes camphor is employed as a mild irritant and antiseptic in an alcohol solution or in ointments. When applied externally, it causes reddening of the skin with a slight irritation of the epidermis. A shortcoming of camphor is its insolubility in water, while oil injections are always painful. This is why camphor is sometimes replaced with drugs having a similar action that are soluble in water such as cordiamin (nikethamide) and corazol (pentetrazole).

Camphor is dispensed in powders, tablets, and in ampoules containing 2 ml of a 20% solution and 1 ml of a 10 or 20% solution

Bromocamphor (*Bromcamphora*)

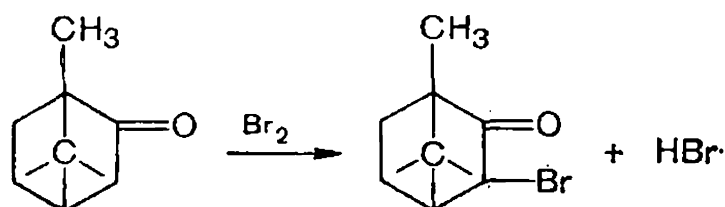


$C_{10}H_{15}OBr$

M.m. 231.14

Bromocamphor is a monohalogen derivative of camphor. The presence of a bromine atom in the molecule underlies the tranquilizing effect of the drug.

Bromocamphor is produced by reacting bromine with camphor in a chloroform solution with heating. The evolving hydrogen bromide HBr is trapped with water:



Bromocamphor forms colourless crystals or a white crystalline powder with a slight smell and taste of camphor. It melts at 74-76 °C.

It dissolves very sparingly in water, and readily in alcohol, ether, chloroform, and fatty oils. It is dextrorotatory.

Bromocamphor is characterized by all the reactions typical of camphor, but a specific reaction is the detecting of bromine after mineralization of the drug, which is achieved by boiling it with a solution of an alkali and zinc dust. After cooling, the bromide ion is determined in the filtrate by conventional analytical reactions.

When the quality of the drug is being tested, the State Pharmacopoeia requires that no hydrohalogen acids or their salts be present. To check this, the drug is agitated with water and filtered. The filtrate should give no reactions for halogens, and the solution should have a neutral reaction.

Quantitative determination consists in finding the bromine content in the drug after mineralization by argentometry (the Volhard method).

Bromocamphor has a tranquilizing action on the central nervous system and improves cardiac activity. It is therefore administered in increased nervous excitation and neurasthenia as a tranquilizer and soporific. It is dispensed as 0.1-0.5-g powders and pills.

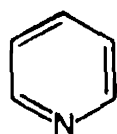
It should be stored in well closed orange glass jars in a place protected from light.

REVIEW QUESTIONS

1. What compounds are called terpenes?
2. How are terpenes classified?
3. How many optically active isomers does menthol have and how can this be explained?
4. What is menthol from the chemical viewpoint?
5. What kind of chemical compound is terpin hydrate?
6. How can the existence of *cis*- and *trans*-isomers of terpin hydrate be explained?
7. How does the introduction of bromine into the camphor molecule affect its pharmacological action?
8. Why can the bromine in a bromocamphor molecule be detected only after mineralization?

Chapter 27. Heterocyclic Compounds

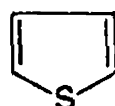
Heterocyclic compounds are compounds whose molecule is a ring (or rings) consisting not only of carbon atoms, but also of other ones, most frequently nitrogen, sulphur, or oxygen:



Pyridine

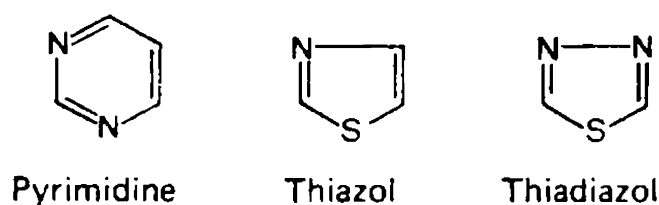


Furan

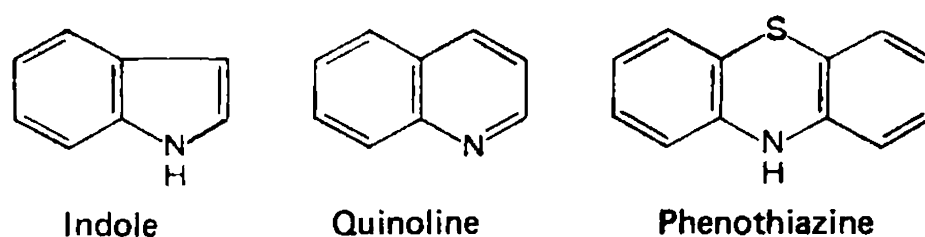


Thiophene

The atoms (except carbon) in a heterocyclic ring, in the given case N, S, and O, are called **hetero atoms** (from Greek *heteros*, other). There are rings with two, three, and more hetero atoms:



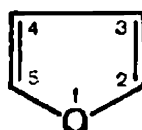
Heterocyclic compounds can be a condensed system of two, three, or four rings:



Many valuable medicaments of both a natural origin (alkaloids, vitamins, antibiotics, enzymes) and of a synthetic one [analgin (novaminsulphon), furacilin (nitrofurazone), barbiturates, cordiamin (nikethamide), dibazole (bendazol), chinosol (8-quinolinol potassium sulphate), aminazine (chlorpromazine)] have a heterocyclic structure.

Heterocyclic compounds are classified according to the nature of the heterocyclic systems whose derivatives they are, for example, derivatives of furan, pyrazol, thiazole (five-membered heterocycles) and derivatives of pyridine, pyrimidine, quinoline (six-membered heterocycles).

27.1. FURAN DERIVATIVES

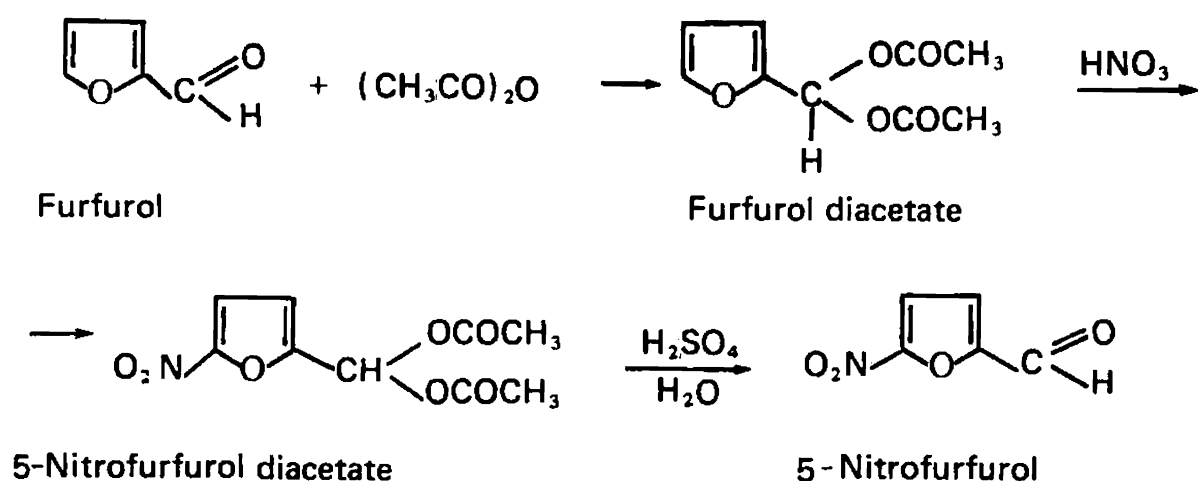


The heteroatom in a furan molecule is oxygen. Furan itself has no physiological activity, but its nitrogen derivatives, especially 5-nitrofurans, have antibacterial activity and are employed in medicine. They suppress the growth of Gram-positive and Gram-negative microbes in quite high dilutions of 1:50 000. They also act on some viruses and Rickettsia. Such a broad spectrum of action of the 5-nitrofurans, their comparatively low toxicity and high stability in storage attracted the attention of chemists and pharmacologists to this class of compounds.

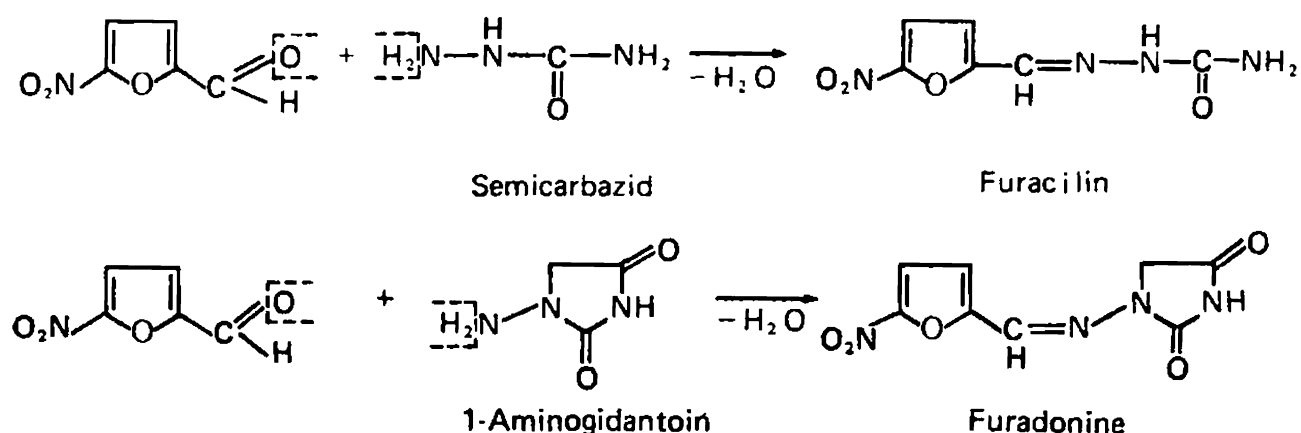
Studying of the chemotherapeutic action of the 5-nitrofurans was begun in the USSR in 1943 at the Institute of Organic Synthesis of the Latvian SSR Academy of Sciences. The work was conducted under the guidance of Academician S. Giller. At this institute, drugs such as furacilin (nitrofural), furadonin (nitrofurantoin) and furazolidone were created. They won widespread recognition and application both in the USSR and in many foreign countries.

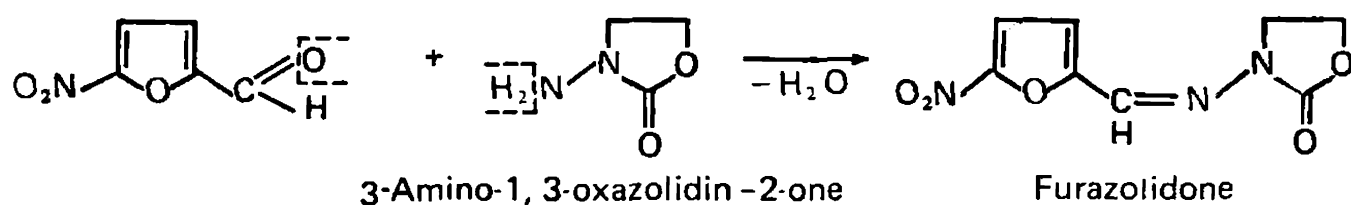
The starting substance for the synthesis of all preparations of the nitrofuran series is furfural, which is abundant and obtained from the residues of various agricultural products (corn cobs, sunflower seed shells, etc.).

The first part of synthesis up to the production of 5-nitrofurfural is the same for all the preparations: the furfural is nitrated with nitric acid in the presence of acetic anhydride, which reacts with the aldehyde group of the furfural and protects it from oxidation by the nitric acid. The resulting 5-nitrofurfural diacetate is hydrolyzed with sulphuric acid to produce 5-nitrofurfural:



The 5-nitrofurfural is further reacted with semicarbazide to form furacilin (nitrofurazone); condensation with 1-aminohydantoin yields furadonin (nitrofurantoin), and so on:





The above preparations are pharmacopoeial ones. Recently, nifuron, furagin, and its soluble potassium salt solafur have been introduced into medical practice (Table 4).

TABLE 4. Selected Derivatives of 5-Nitrofuran Used as Drugs

Name	Structural formula
Furagin	
Solafur-soluble furagin	
Nifuron	

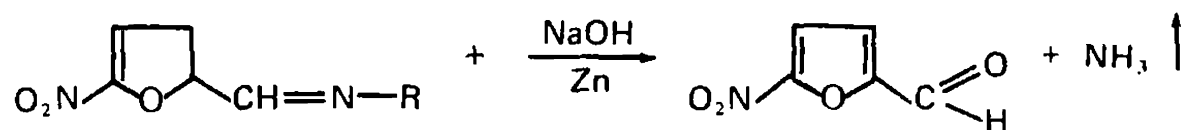
For the preparations of the nitrofuran series to exhibit an antibacterial activity, the nitro group must be only in position 5 of the furan ring. Its transition to another position lowers the physiological activity. The nature and position of the substituent in the furan ring also affect antibacterial activity. Compounds having a side chain in position 2 of the furan ring exhibit the greatest physiological activity.

All the nitrofuran preparations are tasteless or slightly bitter crystalline powders. Depending on the length of the side chain, they are yellow in colour with various tints from light to orange-yellow, reddish- and yellow-brown. Almost all the preparations of this series dissolve poorly in water. Heating increases the solubility. Nitrofurans dissolve somewhat better in alcohol and other organic solvents. They dissolve especially well in dimethylformamide and propylene-

glycol. Nitrofurans are sensitive to light, therefore even their dilute solutions must be protected from daylight. Ultraviolet light causes irreversible decomposition of the molecule, therefore these drugs should be stored in dark glass bottles.

Compounds of the 5-nitrofurans series can be identified by group reactions typical of all the representatives of this series, and by reactions specific for the individual drugs.

The group reactions are: (a) a reaction with solutions of alkalis; most frequently a red or orange-red colour appears whose intensity and nature depend on the structure of the substituent in position 2 of the furan ring. Some compounds produce a colour only in a strongly alkaline medium or only when heated, others produce one when cold; and (b) a reaction of ammonia evolution when alkaline solutions of the drugs are treated with zinc dust with heating:



The specific reactions are: (a) the formation in aqueous solutions of coloured complexes when a drug reacts with a salt of a heavy metal (CuSO_4 , $\text{Co}(\text{NO}_3)_2$, AgNO_3); for example, when a 10% copper sulphate solution and a 10% sodium hydroxide solution are added to an alcohol solution of furacilin, a dark red precipitate forms, of furadonin—a dirty green one forms, of furazolidone—a green one forms; and (b) a reaction with an alcohol solution of an alkali in various organic solvents; most often acetone and dimethylformamide in which nitrofurans dissolve very well are used as these solvents. Depending on the concentration of the drug in the organic solvent and the amount of alkali added, the colours vary for each drug.

Various kinds of chromatography can be used to identify the drugs of the nitrofurans series, and each of the drugs can be characterized by the value of R_f .

The content of drugs of the nitrofurans series can be determined in a variety of ways. Since all the drugs produce coloured solutions with solutions of alkalis, photoelectrocolorimetry can be used as a group method for their quantitative determination. The State Pharmacopoeia recommends determining furadonin and furazolidone in this way.

The iodimetric method is recommended for drugs containing a hydrazine group ($=\text{N}-\text{NH}-$) that can be readily oxidized (for example, furacilin); the bromatometric method can also be used.

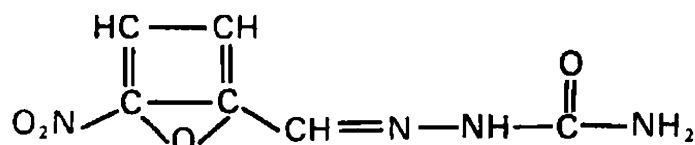
The nitrofurans are widely used in treating various suppurative, inflammatory processes, especially caused by staphylococci and various intestinal bacteria. One of the main indications for the administration of nitrofurans is the antibiotic resistance of the patho-

genes. Nitrofurans have found widespread use in surgery. The drugs are dispensed in powders and tablets.

Drugs of the nitrofuran series should be stored in well closed dark glass bottles in a cool place protected from light. The drugs are listed in Group B.

Furacilin (*Furacilinum*)

Semicarbazone of 5-nitrofurfural



$\text{C}_6\text{H}_6\text{N}_4\text{O}_4$

M.m. 198.14

Furacilin (nitrofural, nitrofurazone) is produced according to the general scheme for 5-nitrofuran drugs.

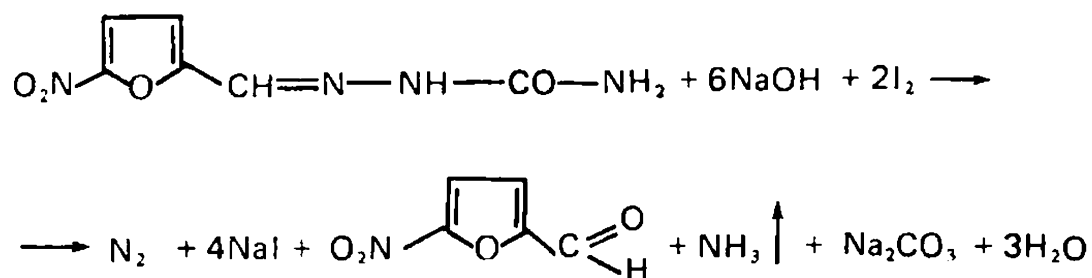
Furacilin is a yellow or greenish-yellow finely crystalline powder with a bitter taste. It dissolves very poorly in water, and poorly in ethanol. It gives all the reactions characteristic of drugs of the nitro-furan series.

The State Pharmacopoeia allows admixtures of chlorides, sulphates, heavy metals, and arsenic in the drug within the tolerated limits.

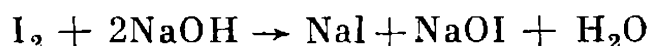
The drug may contain an admixture of semicarbazide, which is determined with a Fehling solution. Since this impurity is not tolerated in the drug, no red precipitate of copper(I) oxide should appear when the Fehling solution is added and the mixture is heated.

The content of the drug is determined iodimetrically. A weighed sample of the drug is dissolved in water with heating in a water bath (70-80 °C). The solubility is improved by adding sodium chloride. Next an excess of a standard iodine solution is added to a definite amount of the mixture, and then 0.1 ml of a sodium hydroxide solution to neutralize the evolving hydroiodic acid.

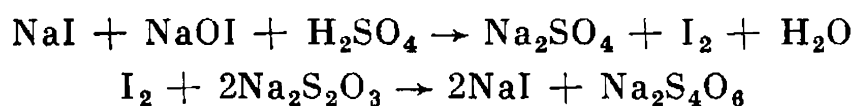
The hydrazine group is oxidized to nitrogen:



But in the alkaline medium the iodine can react with the alkali to yield hypoiodites (NaOI) and iodides (NaI):



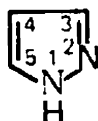
When sulphuric acid is added, iodine evolves, which together with the taken excess of the standard iodine solution is titrated with sodium thiosulphate:



Furacilin is employed as an antibacterial agent for the prophylaxis and treatment of suppurative and inflammatory processes. For example, its aqueous solutions are used for treating suppurative wounds, burns, and in the inflammation of the mucous membranes of the throat (gargling). Furacilin is prescribed for oral administration to treat bacterial dysentery.

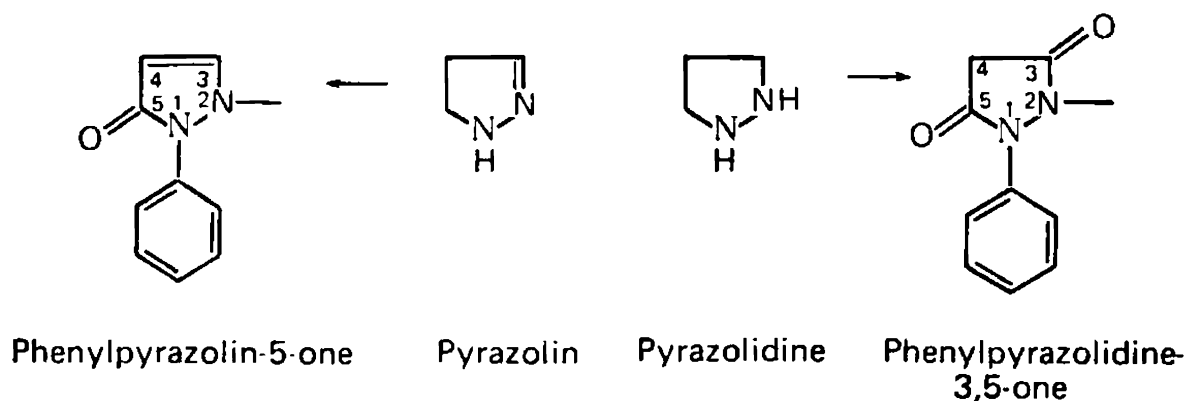
It is dispensed in 0.1-g powders and tablets for oral administration and in 0.02-g ones for preparing solutions for external application.

27.2. PYRAZOL DERIVATIVES



The pyrazol derivatives include widely known drugs, chiefly with an analgesic action such as antipyrine (phenazone), amidopyrine (aminophenazone), analgin (novaminsulphon), and butadion (phenylbutazone).

Pyrazol has an aromatic nature and therefore can participate in substitution reactions. Its double bonds can be hydrogenated partly (pyrazoline) or completely (pyrazolidine):



The ketoderivative of pyrazoline, i.e. 1-phenylpyrazolin-5-one, is the basis of molecules of antipyrine, amidopyrine, and analgin; the diketoderivative of pyrazolidine, i.e. 1-phenylpyrazolidine-3,5-dione forms the structure of the drug butadion.

The nitrogen in position 2 can have various substituents, for example, the phenyl radical in a molecule of 1-phenylpyrazolidine-3.5-dione (butadion), and the methyl radical in a molecule of 1-phenylpyrazolin-5-one (antipyrine, amidopyrine, analgin).

Substituents at the carbon atom in position 4 determine the specific chemical properties and pharmacological action of the pyrazole derivatives. Antipyrine, for example, has hydrogen in position 4. Under the influence of the nearest carbonyl group, the hydrogen is mobile and ensures reactions that are only specific for antipyrine. Amidopyrine, analgin, and butadion have various substituents at the carbon in position 4. They also underlie the specific chemical properties of these compounds.

All the pyrazole derivatives can be oxidized (except for antipyrine); the degree of oxidation differs for each drug and depends on the substituent at the carbon in position 4.

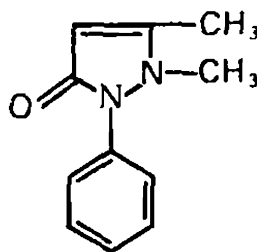
The oxidation products have various colours depending on the oxidizing agent used and the reaction conditions. For example, if sodium nitrite in an acidic medium is added to amidopyrine as an oxidizing agent, a violet colour is observed, whereas a potassium chromate solution produces a brownish-red colour. Such oxidation reactions are employed to identify the given group of drugs.

The readiness of oxidation also requires the corresponding conditions of storage of these drugs, namely, in well closed bottles and in a place protected from light.

All the drugs of this group are produced synthetically.

Antipyrine (*Antipyrinum*)

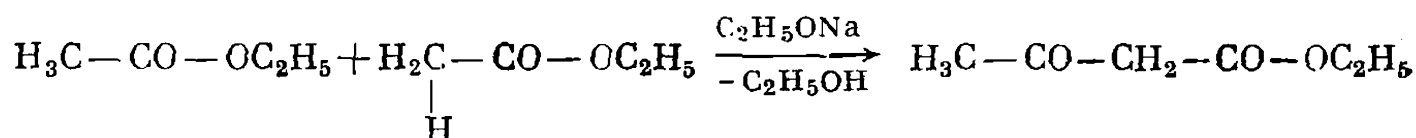
1-Phenyl-2,3-dimethyl-5-pyrazolone



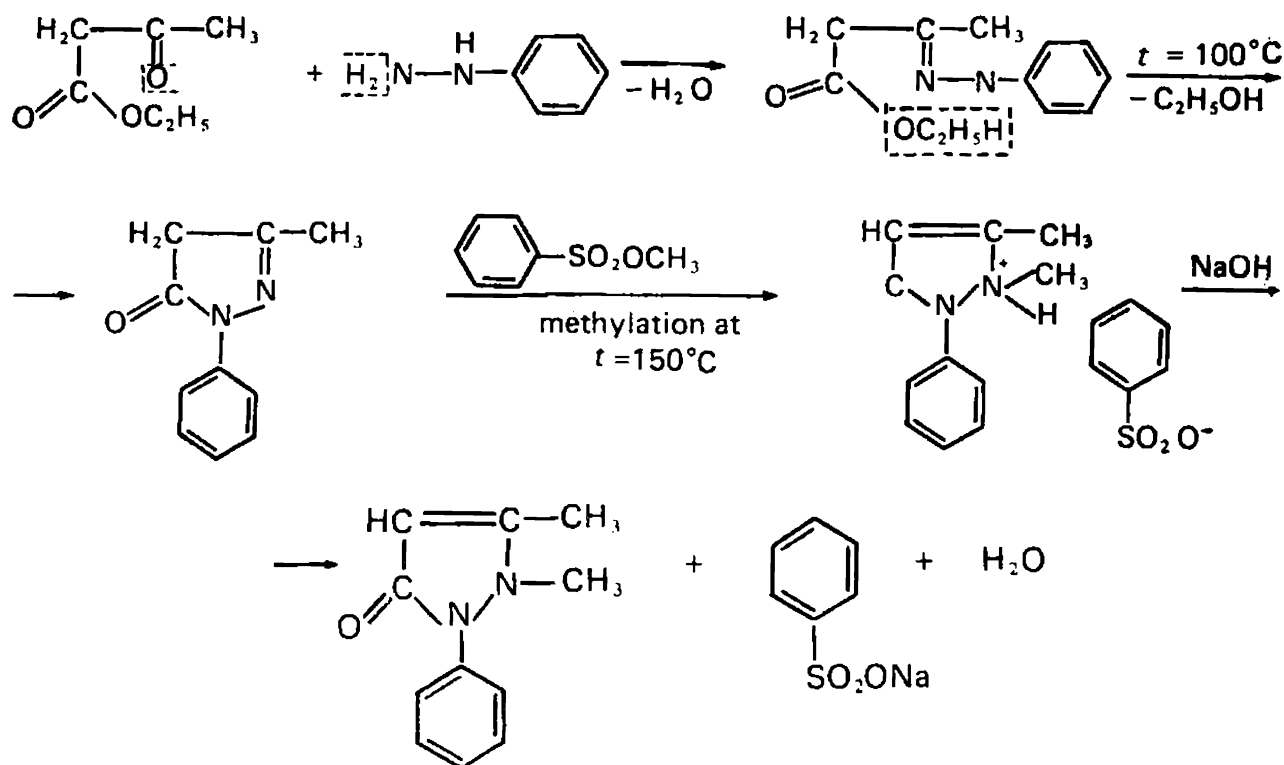
$C_{11}H_{12}N_2O$

M.m. 188.23

The starting substances for the synthesis of antipyrine (phenazone, analgesine) are acetylacetate and phenylhydrazine. Acetylacetate is produced by the condensation of two molecules of ethyl acetate in the presence of sodium ethylate:



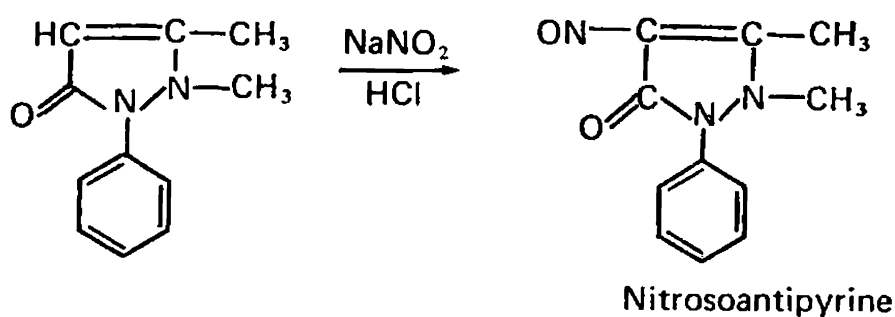
The acetylacetate is reacted with phenylhydrazine:



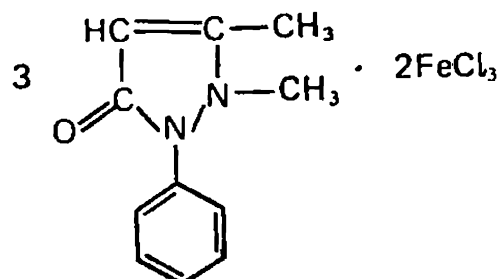
Antipyrine

Antipyrine forms colourless crystals or a white crystalline powder with a slightly bitter taste, without an odour. It dissolves very readily in water, readily in alcohol and chloroform, and sparingly in ether.

The drug is identified by: (a) the formation of nitrosoantipyrine (of an emerald green colour) by reacting the drug with a sodium nitrite solution in an acidic medium:

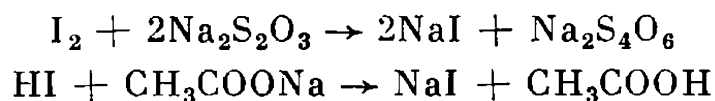
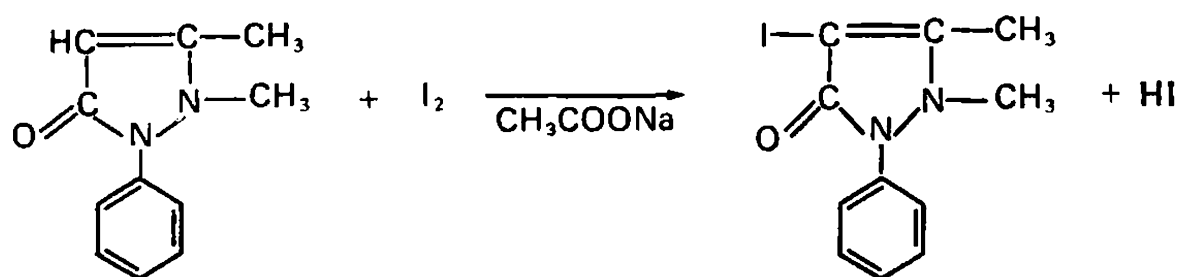


(b) a reaction with an iron(III) chloride solution; an intensive red colour appears owing to the formation of the complex salt ferripyrine:



These reactions are official ones. The melting point of the drug (110-113 °C) can be used to identify it and check its purity.

The content of antipyrine is determined by the iodimetric method based on the ability of antipyrine to react with the halogens owing to the mobile hydrogen in position 4 of the molecule. A weighed sample of the drug is titrated with iodine in the presence of sodium acetate that binds the evolving hydroiodic acid and thus prevents the reversible reaction:



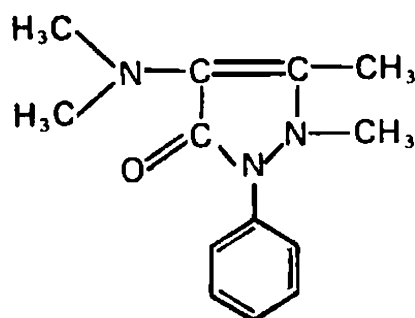
The iodopyrine formed in the reaction can adsorb a certain amount of iodine on its surface, therefore alcohol or chloroform is added to dissolve the formed iodopyrine.

Antipyrine is employed as an antipyretic, analgesic, and tranquilizing drug in the treatment of headaches, neuralgia, and rheumatism. It is dispensed in 0.25-g powders and tablets.

Antipyrine can readily react with acids, phenols, aldehydes, and mercury salts. When reacting with some of these substances, antipyrine becomes liquid, which must be taken into consideration when writing prescriptions. It is listed in Group B.

Amidopyrine (*Amidopyrinum*)

1-Phenyl-2,3-dimethyl-4-dimethylamino-5-pyrazolone

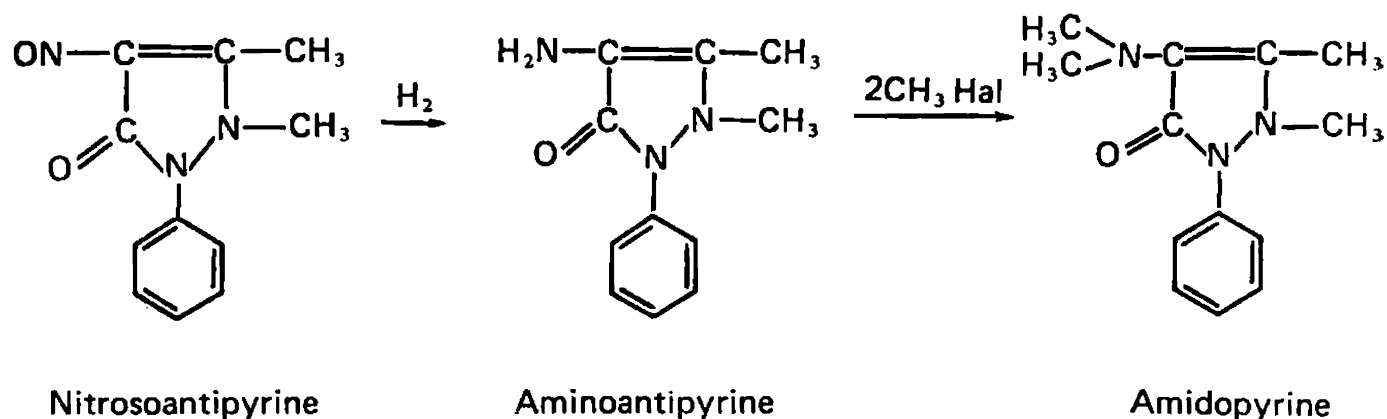


$\text{C}_{13}\text{H}_{17}\text{N}_3\text{O}$

M.m. 213.30

Amidopyrine (aminophenazone, amidofebrin, amidofen) is produced from antipyrine by introducing a dimethylamino group into its molecule at position 4. First nitrosoantipyrine is obtained. It is

then reduced to aminoantipyrine, and the latter is methylated, the product being amidopyrine:



Amidopyrine forms odourless white crystals or a white crystalline powder with a slightly bitter taste. It dissolves readily in chloroform, is soluble in ether, ethanol, and dissolves slowly in water (1:20).

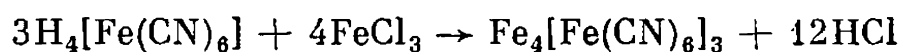
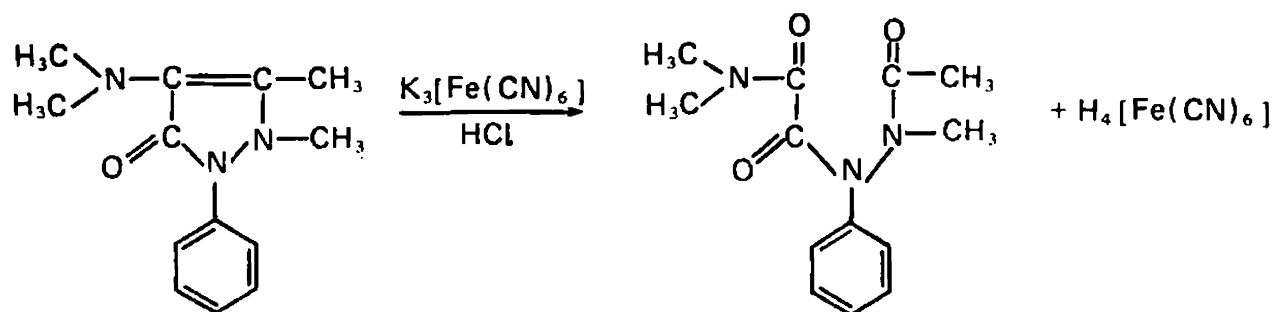
Aqueous amidopyrine solutions have a weakly alkaline reaction. The dimethylamino group in the amidopyrine molecule imparts basic properties to it, therefore it forms salts with acids.

Amidopyrine is a good reducing agent and is itself readily oxidized by oxidizing agents such as iron(III) chloride, silver nitrate, and potassium permanganate. The oxidation products have a variety of colours, consequently these reactions are used to identify the drug:

(a) a reaction with an iron(III) chloride solution yields a violet colour that does not disappear when a mineral acid is added, unlike analgin;

(b) a reaction with a silver nitrate solution first yields a blue-violet colour (the product of oxidation of the amidopyrine), and then a dark precipitate of the reduced silver forms;

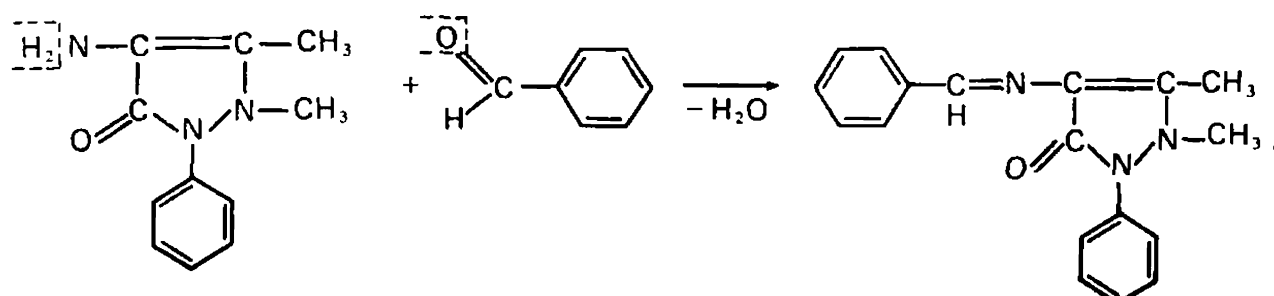
(c) when a solution of potassium ferricyanide $K_3[Fe(CN)_6]$ in an acidic medium is added to a solution of the drug, and then an iron(III) chloride solution, a blue colour appears (Berlin blue). This reaction distinguishes amidopyrine from antipyrine. It is presumed that the action of strong oxidizing agents in an acidic medium causes amidopyrine to become oxidized to dihydroxyamidopyrine:



Berlin blue

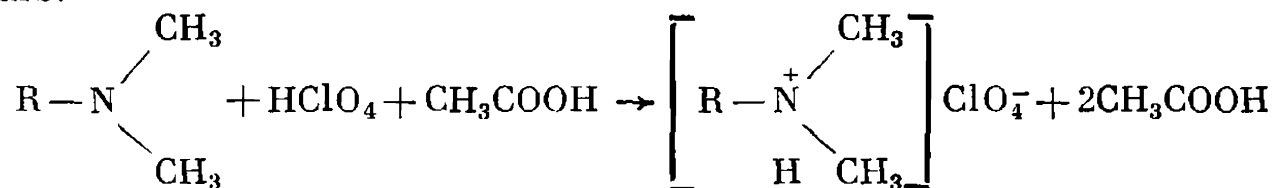
All these reactions are official ones.

The drug may contain admixtures of chlorides (not tolerated by the State Pharmacopoeia) and aminoantipyrine. The latter is allowed by the State Pharmacopoeia within the limits tolerated by the relevant standard. Aminoantipyrine is detected by the turbidization of an aqueous solution of the drug when a benzaldehyde solution is added:



The State Pharmacopoeia recommends acid-base titration in non-aqueous media for the quantitative determination of the drug.

Amidopyrine as a weak base is titrated with perchloric acid in the presence of a protogenic solvent—glacial acetic acid, using a tropeolin-00 indicator in methanol, until a bright violet colour appears:



(R is the residue of the amidopyrine molecule).

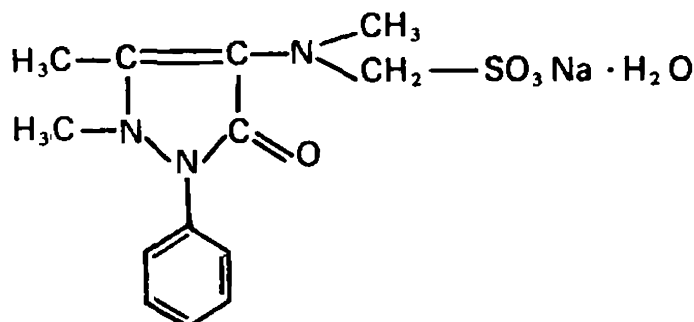
Amidopyrine is a constituent of a large number of medicinal forms and is employed as an antipyretic and analgesic agent. It also produces a number of undesirable side effects. Its prolonged use may sometimes lead to agranulocytosis.

It is dispensed as 0.25-g powders and tablets, and also in the form of 1% and 4% solutions in ampoules, for dissolving penicillin.

It should be stored in well closed jars in a place protected from light. It is listed in Group B.

Analgin (*Analginum*)

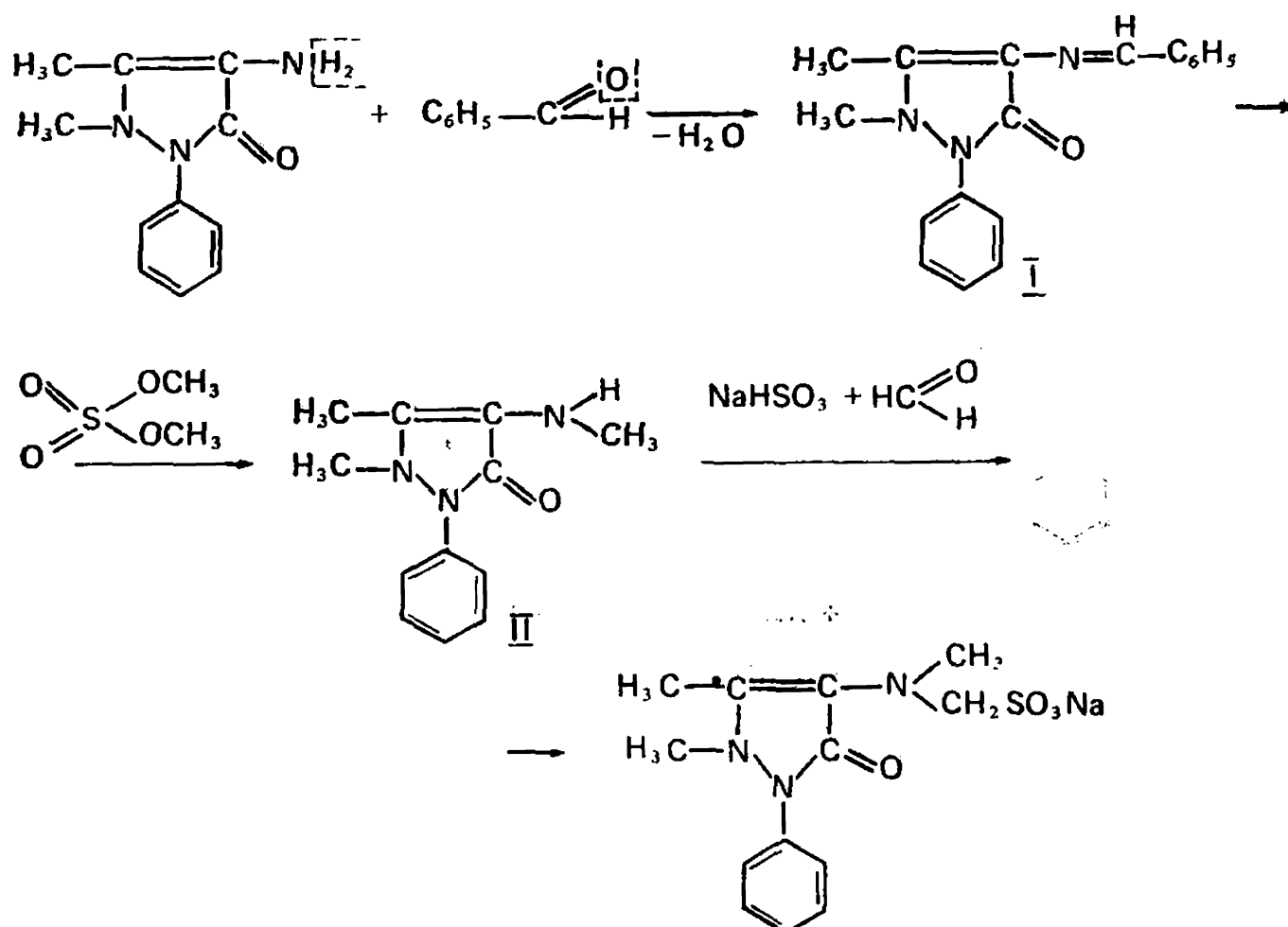
Sodium 1-phenyl-2,3-dimethyl-4-methylamino-5-n-pyrazolonmethanesulphonate





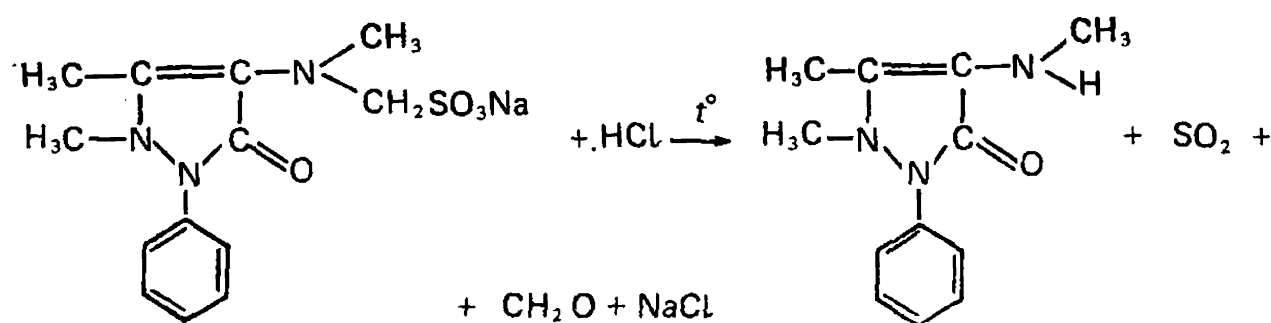
M.m. 351.36

Analgin (novaminsulphon, dipyrone) is synthesized from aminoantipyrine, which is reacted with benzaldehyde. The resulting benzylidene-aminoantipyrine (I) is methylated with dimethylsulphate to produce monomethylantipyrine (II). Treatment of the latter with a mixture of aqueous solutions of formaldehyde and sodium hydrogen sulphite yields analgin:



Analgin is an odourless white coarsely acicular crystalline powder, sometimes with a hardly noticeable yellowish tint, having a bitter taste. It dissolves readily in water, sparingly in alcohol, and does not dissolve in ether, chloroform, and acetone. Aqueous solutions turn yellow when left in the air.

The drug is identified by: (a) a reaction with mineral acids with heating; a smell of sulphur dioxide and then of formaldehyde (the products of decomposition of sodium methylenesulphite) is felt:

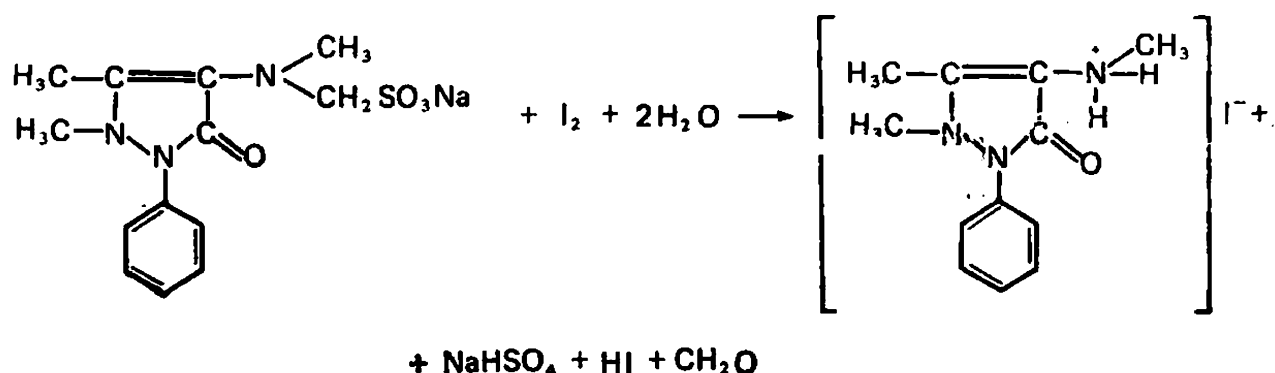


(b) the coloured oxidation products; when an oxidizing agent such as potassium iodate is added to an acidified solution of the drug in an alcohol medium, the solution turns crimson (oxidation intermediates). When more potassium iodate is added, the colour becomes more intense and a brown iodine precipitate separates:



These reactions are official ones and distinguish analgin from antipyrine and amidopyrine. The State Pharmacopoeia tolerates admixtures of heavy metals and arsenic in the drug within the specified limits and does not tolerate admixtures of aminoantipyrine.

The quantitative determination of the drug is based on the oxidation of its molecule by iodine (the sulphite ion transforms into a sulphate ion):



A weighed sample of the drug dissolved in water is titrated with iodine until an unvanishing yellow colour of the solution appears.

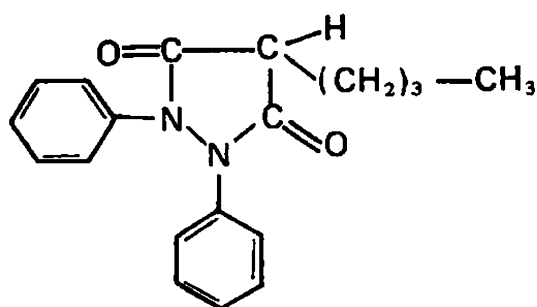
Analgin is employed as an analgesic, antipyretic, and antiphlogistic agent for the relief of headaches, neuralgia, radiculitis, influenza, and rheumatism.

It is dispensed as 0.25- and 0.5-g powders and tablets, and as a 50% solution in ampoules.

Analgin should be stored in well closed jars in a place protected from light. It is listed in Group B.

Butadion (*Butadionum*)

1,2-Diphenyl-4-n-butyl 3,5-pyrazolidinedione

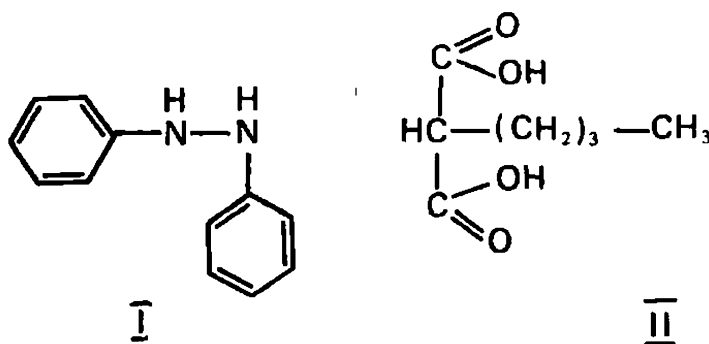


$\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_2$

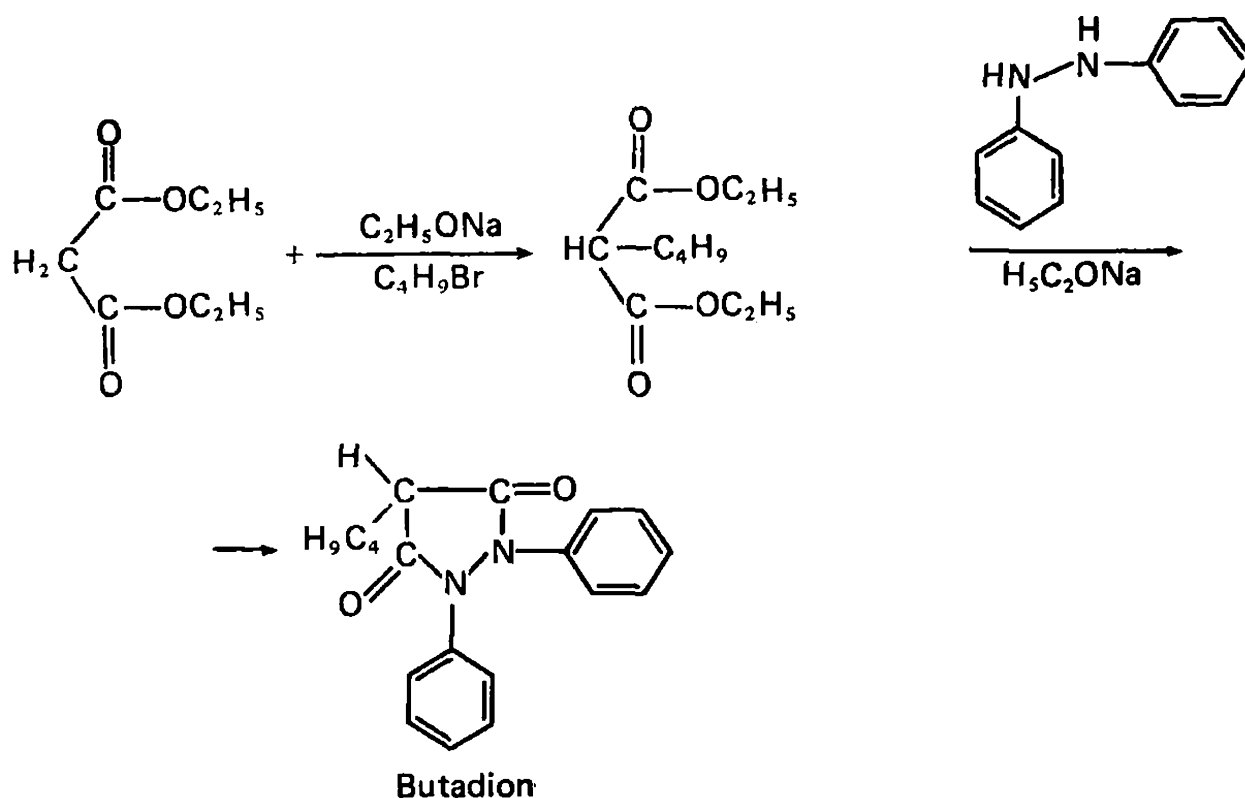
M.m. 308.38

The main part of the butadion (phenylbutazone, diphebutol) molecule is a completely hydrogenated pyrazole—pyrazolidine.

The molecule has two phenyl radicals at the nitrogen atoms in positions 1 and 2. This half of the molecule can be considered as a residue of hydrazobenzene (I). The other half of the molecule can be considered as a part of a malonic acid molecule in which one hydrogen atom in the methylene group has been replaced by a butyl residue (II):



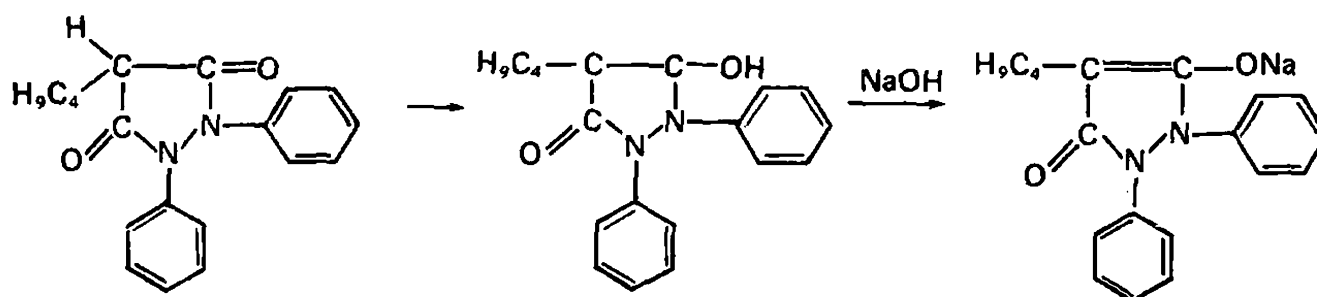
To produce butadion, an *n*-butyl radical is introduced into a malonic ester with the aid of butyl bromide in the presence of sodium ethylate. The resulting *n*-butylmalonate is condensed with hydrazobenzene (I) in the presence of condensing agents; the product is butadion:



Butadion is a white powder, sometimes with a slightly yellowish tint. It is virtually insoluble in water, sparingly soluble in alcohol, and readily in chloroform, ether, and acetone.

Butadion has acidic properties due to the mobile hydrogen (at the carbon in position 4) which can produce an enol form with the

nearest carbonyl groups. As a result, butadion can dissolve in alkalies with the formation of salts:



The sodium salt of butadion dissolves well in water and is used in medicine in the form of solutions in ampoules.

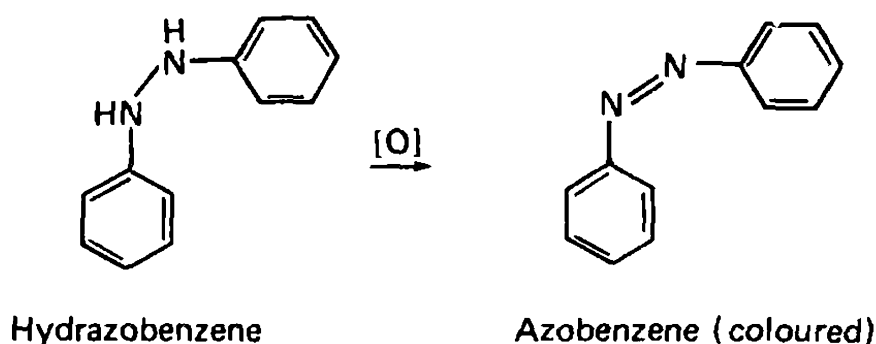
Butadion is readily brominated, the hydrogen atom in position 4 being substituted by bromine.

Butadion yields coloured salts insoluble in water with solutions of the salts of heavy metals. The butadion is first neutralized with an alkali (according to an indicator) up to the formation of a sodium salt, and then, when a copper sulphate solution is added, a copper salt of butadion forms with a gray colour transforming into pale light blue.

A white precipitate of a silver salt forms with a solution of silver nitrate, and a brown precipitate forms with an iron(III) chloride solution.

The basic properties of butadion are expressed weakly (they are weakened by two phenyl radicals). As a base, butadion reacts only with concentrated sulphuric acid.

Butadion can be readily oxidized owing to the hydrazobenzene residue in its molecule:



These properties of butadion determine its identification reactions:

(a) when butadion is oxidized with sodium nitrite in concentrated sulphuric acid, an orange colour appears that transforms to a cherry red one; this is attended by the evolution of gas bubbles. This reaction can be used to detect butadion in the presence of amidopyrine, in a mixture with which it is dispensed;

(b) with a copper sulphate solution, a precipitate of a coloured copper salt of butadion forms.

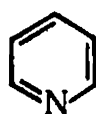
An admixture of hydrazobenzene in the drug is not tolerated. It can be detected by a reaction with a 10% iron(III) chloride solution in the presence of concentrated sulphuric acid (a cherry red colour appears).

Butadion is determined quantitatively by neutralization owing to its acidic properties. A weighed sample of butadion dissolved in acetone (to avoid hydrolysis of the formed sodium salt) is titrated with an alkali using a phenolphthalein indicator.

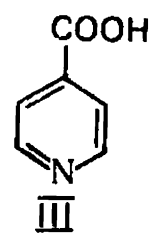
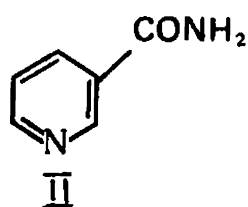
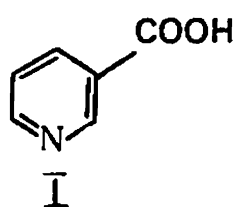
A solution of the sodium salt of butadion becomes yellow when boiled, therefore the aseptic preparation of injection solutions is recommended.

The drug is dispensed in 0.15-g tablets and powders. It is employed as an analgesic, antipyretic, and antiphlogistic agent.

27.3. PYRIDINE DERIVATIVES



Pyridine is a six-membered heterocycle with one heteroatom in the ring, namely, nitrogen. It is not used in medicine owing to its high toxicity, although it is a potent bactericide. The introduction of a number of functional groups into the pyridine ring lowers its toxicity, and therefore some of its derivatives are employed as drugs with a various physiological action, for example, nicotinic acid (I) and its amide (II):

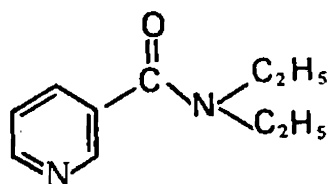


These compounds are a pellagra-preventing (P-P) factor. The amide is a vitamin substance in the vitamin B₂ complex.

The derivatives of 3-pyridinecarboxylic acid (III), namely, isoniazide, ftivazide, saluzide (opiniazide), etc. are a group of antituberculous agents. The pyridine ring is a part of many natural medicaments such as alkaloids and vitamins.

The diethylamide of nicotinic acid is a very important compound. It is used to produce the drug cordiamin (nikethamide). The latter has a stimulating action on the central nervous system, chiefly on the vasomotorial and respiratory centres of the medulla oblongata.

Diethylamide of Nicotinic Acid
(*Diaethylamidum acidi nicotini*)

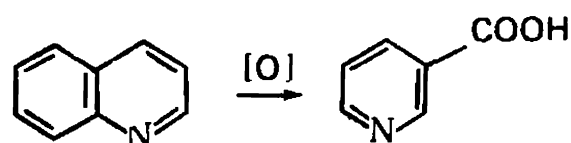


$C_{10}H_{14}N_2O$

M.m. 178.24

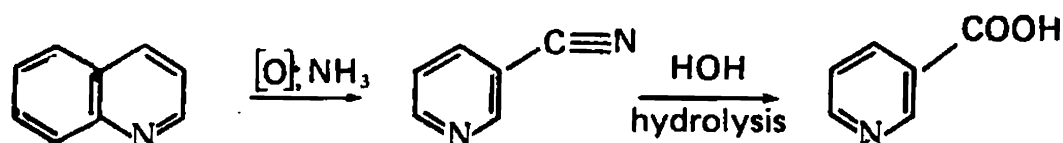
The diethylamide of nicotinic acid is produced from nicotinic acid. The latter can be prepared in two ways:

(1) catalytic oxidation of quinoline in the gaseous phase:



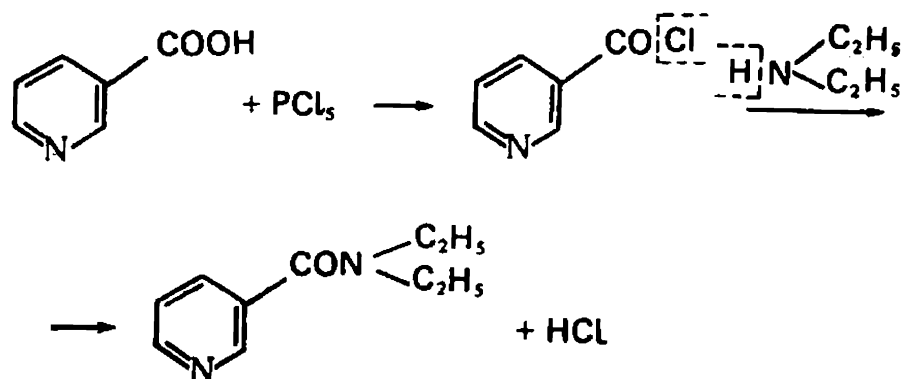
Fused vanadium oxides are used as the catalyst;

(2) the oxidation ammonolysis of quinoline (in the presence of ammonia); the product is nitrile, which after hydrolysis forms nicotinic acid:



The addition of ammonia suppresses oxidation of the pyridine ring. At present, these methods of producing nicotinic acid are commercial ones.

The nicotinic acid is transformed by the action of phosphorus pentachloride into the chloranhydride, which is reacted with diethylamine in the presence of water-removing agents:

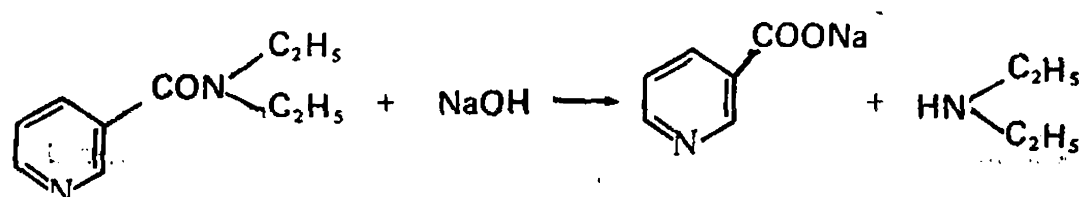


The diethylamide of nicotinic acid is a colourless slightly yellow oily liquid with a weak peculiar odour. It mixes with water, 95% alcohol, ether, and chloroform in all proportions. Its specific gravity is 1.058-1.066.

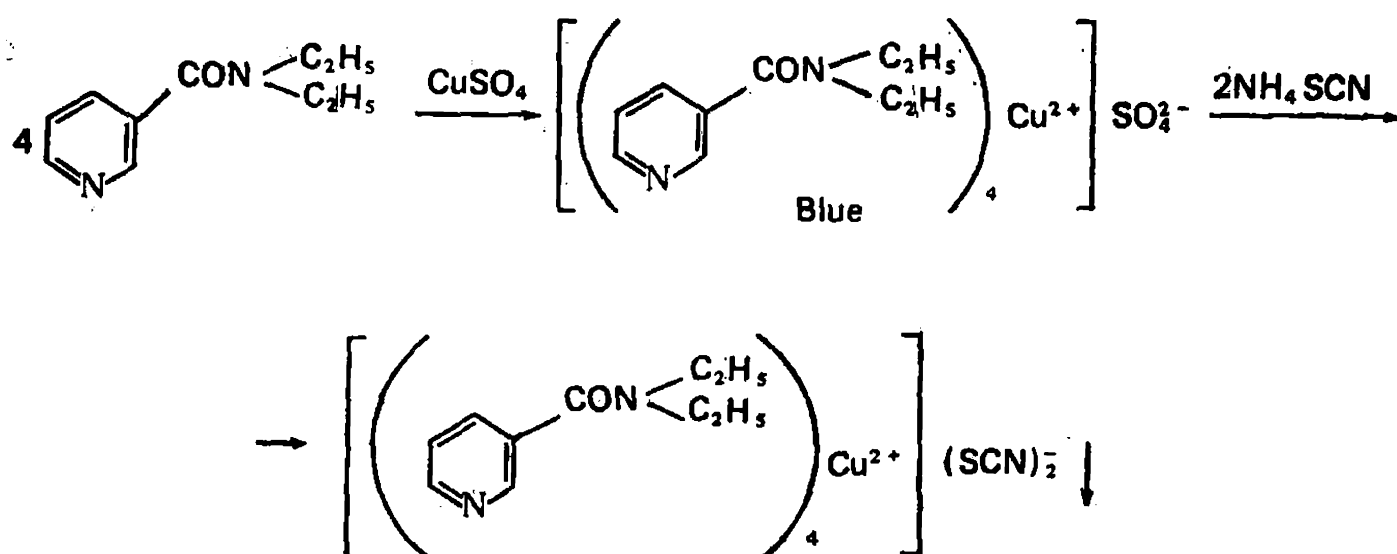
Its pharmacopoeial preparation is cordiamin (*Cordiaminum*), which is a 25% aqueous solution of the diethylamide of nicotinic acid. It is a colourless or slightly yellow liquid with a specific odour.

The identification reactions for the diethylamide of nicotinic acid and cordiamin are the same:

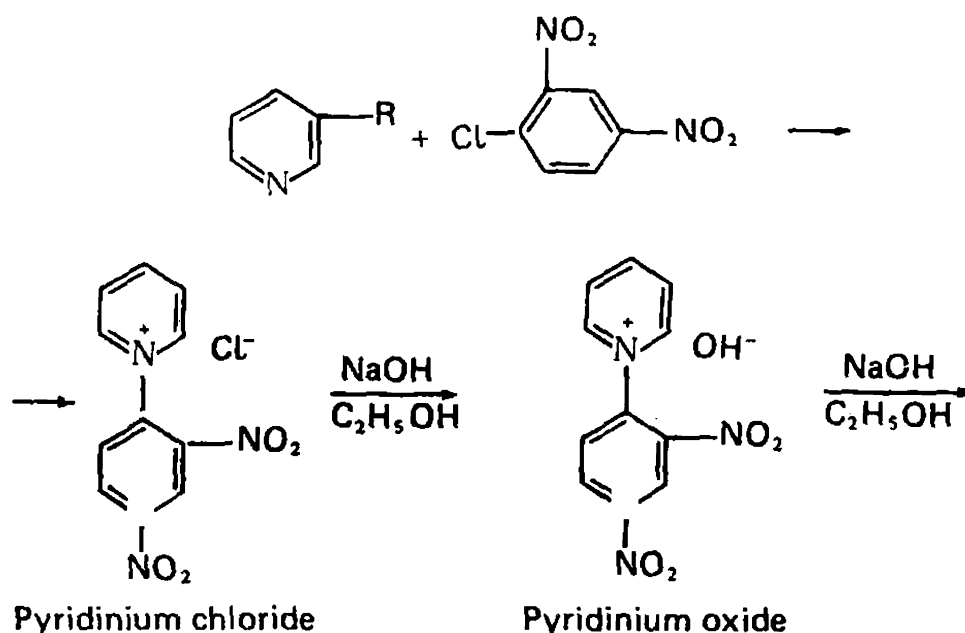
(a) when cordiamin is reacted with a sodium hydroxide solution and heated, diethylamine forms, which has a typical odour of amines:

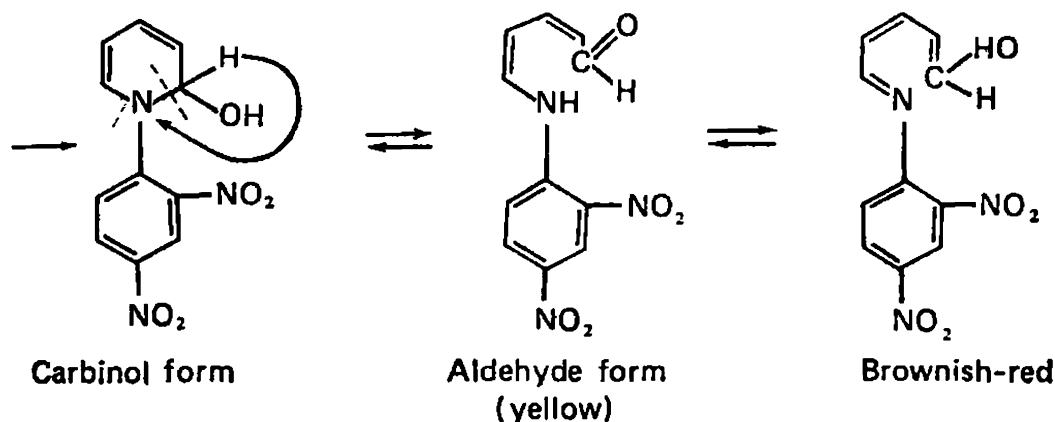


(b) when a copper sulphate solution is added to a solution of the drug, a deep blue colour appears; when an ammonium thiocyanide solution is added, a bright green precipitate forms:



(c) when a solution of the drug is boiled with an alcohol solution of 2,4-dinitrochlorobenzene, the solution turns yellow. After cooling and the addition of a sodium hydroxide solution, a violet colour appears, which gradually turns brownish-red when more alkali is added (a reaction for the pyridine ring):





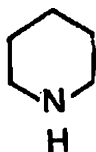
All these reactions are official ones.

To confirm the tertiary nitrogen in the pyridine ring, reactions with complex acids such as phosphatomolybdic and phosphatotungstic acids can be carried out. Coloured precipitates form. The drug may contain reducing substances and organic impurities that are tolerated by the State Pharmacopoeia within the established limits.

The content of the diethylamide of nicotinic acid is determined relative to the nitrogen by the Kjeldahl method. The content of the diethylamide of nicotinic acid in the drug cordiamin is determined by refractometry according to the refractive index.

Cordiamin is administered in acute and chronic disorders of cardiac activity and weakening of respiration. It is prescribed for subcutaneous, intramuscular, intravenous, and also for oral administration. It is dispensed in 1- or 2-ml ampoules for injections and in bottles containing 30 or 10 ml for oral use. Cordiamin should be stored in orange glass bottles with ground glass stoppers. The drug for injections is stored in sealed ampoules in a place protected from light. It is listed in Group B.

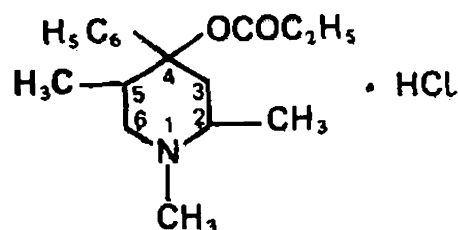
27.4. PIPERIDINE DERIVATIVES



Piperidine is hydrogenated pyridine and also belongs to the six-membered heterocycles.

The piperidine ring is contained in the molecules of many synthetic and natural medicaments. One of the synthetic derivatives of piperidine is the drug promedol (trimeperidine hydrochloride), which was developed when searching for analogues of morphine.

Promedol has found widespread use in medicine as an analgesic replacing morphine. It is a pharmacopoeial drug.

Promedol (*Promedolum*)*1,2,5-Trimethyl-4-phenyl-4-propionyloxypiperidine hydrochloride* $C_{17}H_{25}NO_2 \cdot HCl$

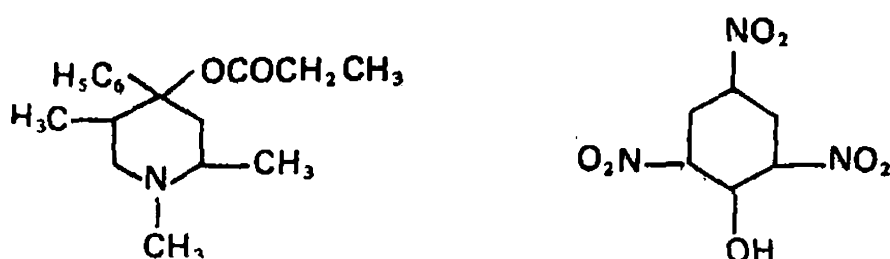
M.m. 311.85

In the chemical respect, promedol (trimeperidine hydrochloride) is an ester of phenyltrimethylpiperidol with propionic acid. Promedol is a white crystalline powder with a bitter taste. It dissolves readily in water and chloroform, is soluble in alcohol, and insoluble in ether and benzene.

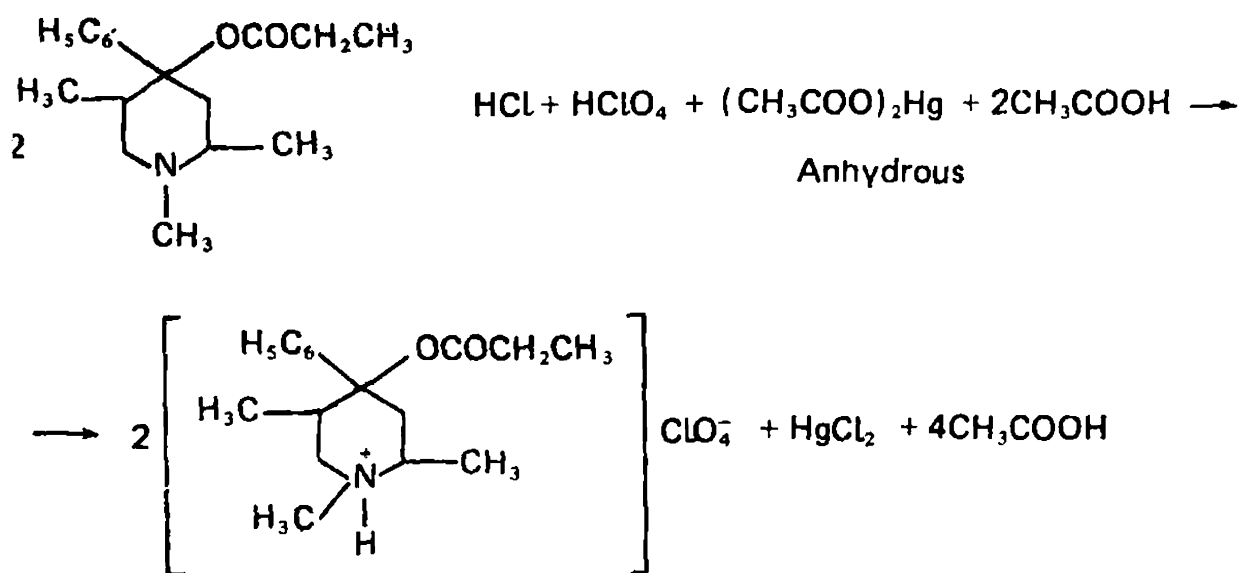
The State Pharmacopoeia recommends the following reactions for identifying the drug:

(a) a reaction with formaldehyde and concentrated sulphuric acid in chloroform, a red ring forms at the phase interface (a reaction for the phenyl radical);

(b) a reaction of formation of a yellow picrate (promedol contains tertiary nitrogen and like a base can form salts with acids, in the given case with picric acid, trinitrophenol):



The drug is determined quantitatively by non-aqueous titration in a medium of glacial acetic acid, the titrant being perchloric acid and the indicator—crystal violet:

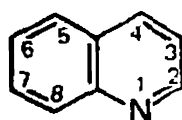


In its analgesic action, promedol is very similar to morphine. It is endured better than morphine and omnopone, does not cause vomiting or constipation, and simultaneously has a spasmolytic action. However, promedol retains the same shortcoming as morphine, i.e. the organism gets accustomed to it upon continuous use.

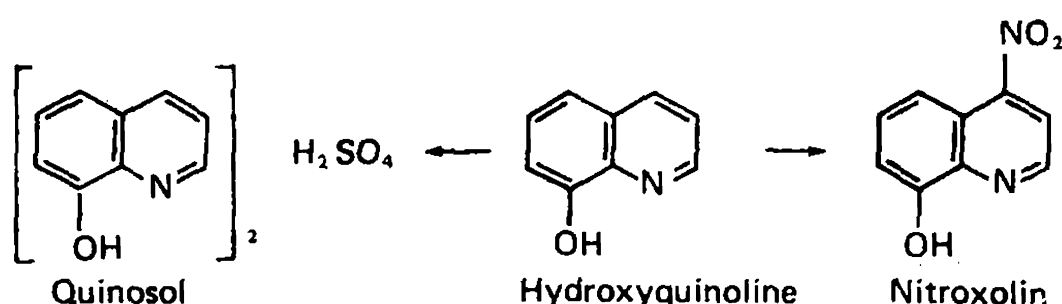
It is dispensed in 0.025-g powders and tablets, and in ampoules containing 1 ml of a 1% or 2% solution.

It should be stored under a lock in well closed jars and sealed ampoules. It is listed in Group A.

27.5. QUINOLINE DERIVATIVES

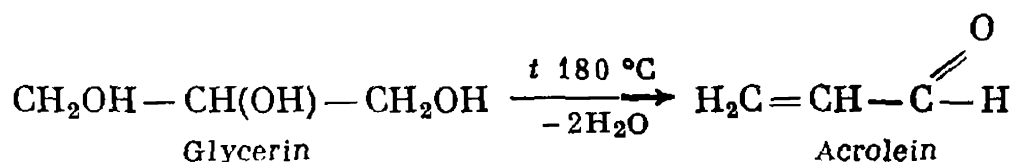


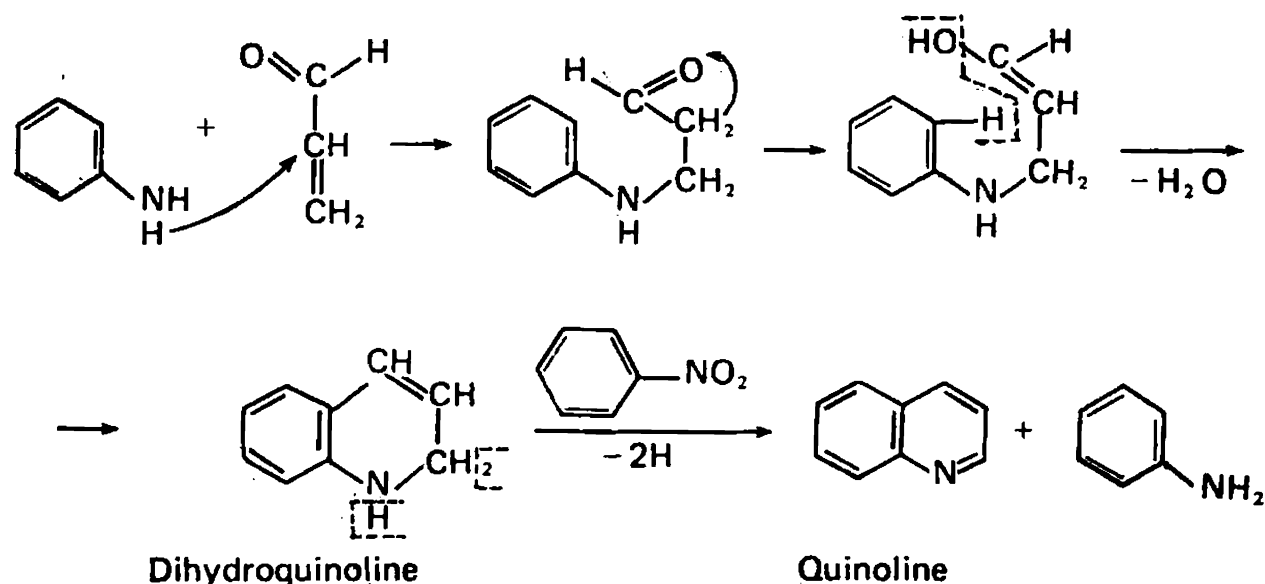
Quinoline, or benzopyridine, has a bactericidal, antiseptic, and antipyretic action, but these valuable properties cannot be used in medicine owing to its high toxicity. The introduction of various substituents into the quinoline molecule, however, lowers its toxicity. A number of quinoline derivatives are known that are employed in medicine as drugs with a various physiological activity, namely, derivatives of 8-aminoquinoline—plasmocid, quinocide (chinocide), and of 4-aminoquinoline—qingamine (chloroquine diphosphate) (antimalarial drugs); derivatives of 4-quinolincarboxylic acid—sovaine (cinchocaine) (a local anaesthetic); and derivatives of 8-hydroxyquinoline—quinosol (chinosol), nitroxoline (5-NOK), enteroseptol (clioquinol) (antibacterial and antiseptic drugs):



The molecules of this group of compounds contain an 8-hydroxyquinoline ring, therefore their synthesis follows the same scheme known as the classical method of quinoline synthesis after Z. Skraup.

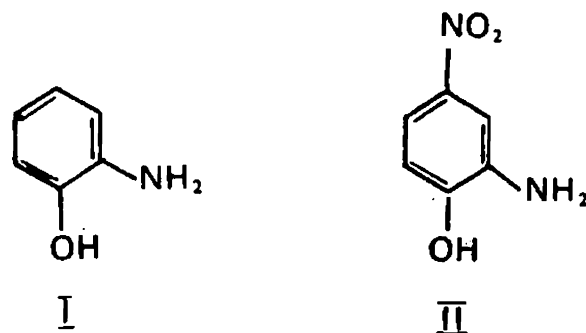
This method consists in heating aniline with glycerin, sulphuric acid, and nitrobenzene. The glycerin is preliminarily dehydrated to acrolein by heating to 180 °C:





The aniline produced together with the quinoline is recycled for condensation with acrolein.

The Skraup method can be used to produce any quinoline derivative if the relevant amine with various substituents is taken as the starting substance. For example, to produce quinosol (8-hydroxyquinoline), ortho-hydroxyaniline (I) should be taken as the starting substance, and to produce nitroxoline, 4-nitro-8-hydroxyaniline (II) should be taken:

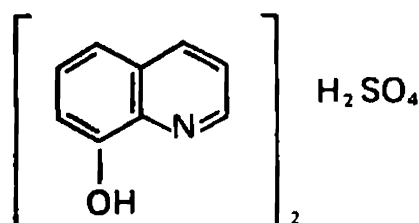


The next synthesis steps repeat those for quinoline.

This is what forms the universal nature of the Skraup synthesis, and it therefore has a practical significance up to the present time.

Quinosol (*Chincolum*)

8-Hydroxyquinoline sulphate



$(C_9H_7NO)_2 \cdot H_2SO_4$

M.m. 388.40

To produce quinosol (chinosol) by the Skraup method, 8-hydroxyquinoline is first produced. It is dissolved in alcohol and treated

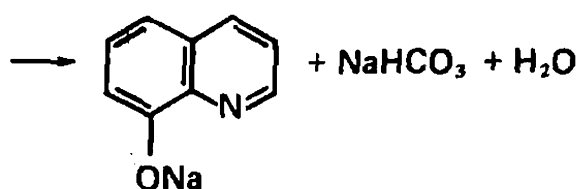
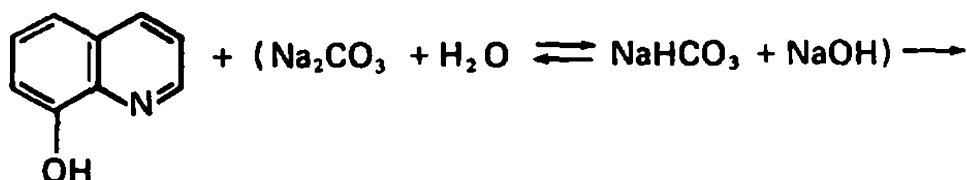
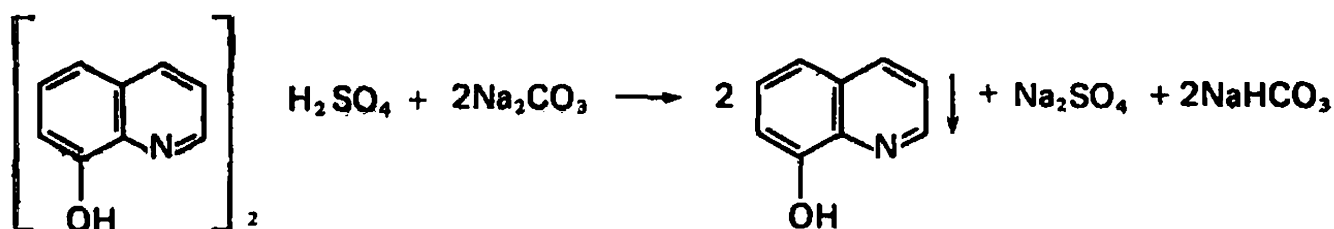
with a calculated amount of sulphuric acid. The latter forms a salt owing to the basic properties of the tertiary nitrogen of 8-hydroxyquinoline.

Quinosol is a finely crystalline lemon-yellow powder with a specific odour. It dissolves readily in water, only slightly in alcohol, and is insoluble in ether and chloroform. The drug melts at 175-178 °C. It is identified as follows:

(a) by a reaction with a barium chloride solution; a white precipitate of barium sulphate forms (a reaction for SO_4^{2-});

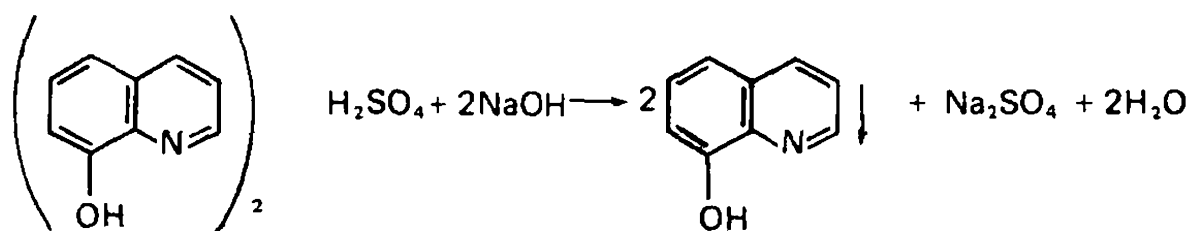
(b) by a reaction with an iron(III) chloride solution; a bluish-green colour appears (the phenol hydroxyl group);

(c) by precipitation with a sodium carbonate solution of a quinosol base that is soluble in an excess of the reagent:



Soluble sodium quinolate

The State Pharmacopoeia recommends determining the content of quinosol in the drug by neutralization. A weighed sample of the drug dissolved in water is titrated with an alkali in the presence of chloroform, which extracts the formed base:



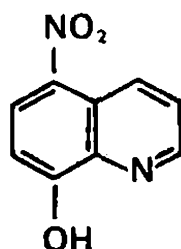
Quinosol is used as an antiseptic in a dilution of 1:1000 and 1:2000 for the disinfection of hands, washing wounds and sores, and for irrigation.

Quinosol must never be used to disinfect surgical instruments because it forms insoluble compounds with metals.

The drug should be stored in tightly closed containers.

Nitroxoline (*Nitroxolinum*)

5-Nitro-8-hydroxyquinoline



$C_9H_6N_2O_3$

M.m. 190.16

Nitroxoline (5-NOK) is a finely crystalline yellow or grayish yellow powder; it may have a light greenish tint.

The drug is identified by:

(a) a reaction with an iron(III) chloride solution; a green colour appears (8-hydroxyquinoline);

(b) an ultraviolet absorption spectrum of a 0.001 % solution of the drug in 95 % alcohol in the region of 220-460 nm. There are three peaks in this region, namely, at 242 ± 2 nm, 356 ± 2 nm, and 455 ± 2 nm;

(c) a reaction of reducing the nitro group to an amino group with the subsequent formation of an azo dye (see Chap. 23), which is coloured orange-red.

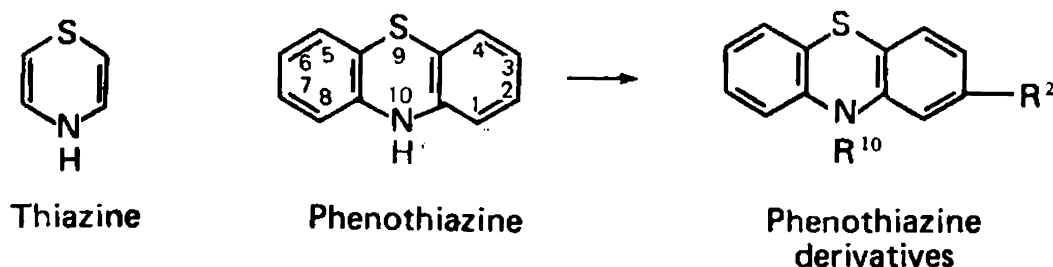
The content of nitroxoline in the drug is determined by acid-base titration in non-aqueous media. The drug is dissolved in formic acid and titrated with a 0.1 *N* perchloric acid solution using a malachite green indicator (a 0.5 % solution in glacial acetic acid) until a yellow colour appears. At the end of titration, five drops of the indicator are added. The calculation is performed for the dry substance. The nitroxoline in the drug can also be determined quantitatively by nitritometry after reducing the nitro group to an amino group.

Nitroxoline is administered as an antibacterial agent in infections of the urogenital tract (pyelonephritis, cystitis, etc.).

It is dispensed in 0.05-g spherical tablets. It should be stored in a dry place protected from light.

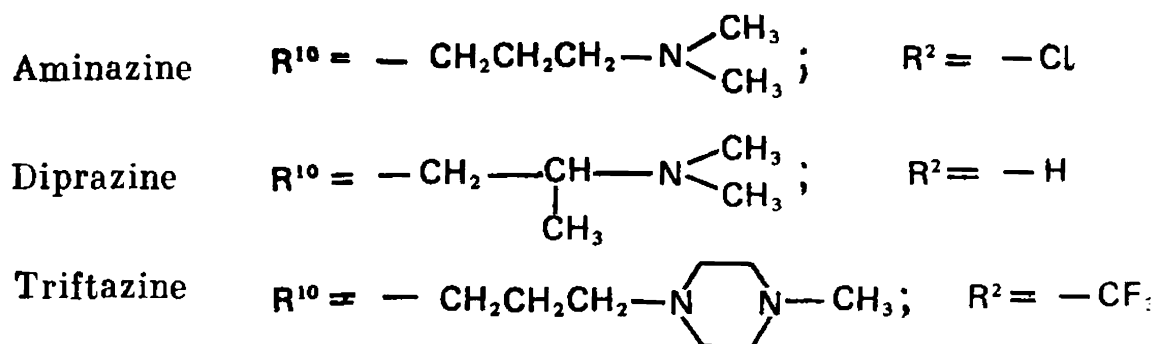
27.6. PHENOTHIAZINE DERIVATIVES

The phenothiazine nucleus is a condensed system of three rings, namely, thiazine and two benzene rings bound to it, hence phenothiazine can be called a dibenzoderivative of thiazine:



Although phenothiazine does exhibit a physiological activity (anthelmintic action and local anaesthetic), at present it has lost its significance as a drug.

Phenothiazine derivatives having substituents (R^2 and R^{10}) in positions 2 and 10 of the nucleus are of much greater significance. Most frequently R^{10} is a residue of 3-dialkylaminopropanol ($-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{N}<$) or its derivatives, while R^2 can be H, Cl, COCH_3 , CF_3 , etc.:



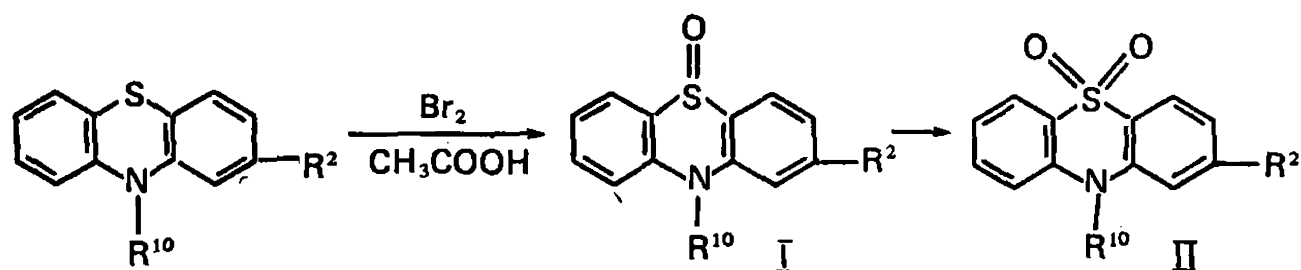
Such phenothiazine derivatives unite a large group of drugs with a psychotropic action (neuroleptics).

All these drugs are similar to one another in their appearance. They are mostly white, with or without a creamish tint, crystalline powders. Some of them have a greenish-yellow colour [triftazine (trifluoperazine), mepazine (pecazine)]. They dissolve very readily in water, readily in 95% alcohol and chloroform; they are practically insoluble in ether and benzene.

As regards the chemical properties of the phenothiazine derivatives, they can be readily oxidized. Depending on the nature of the oxidizing agent (bromine water, nitric and sulphuric acids, iron(III) chloride, etc.), the oxidation products have different colours. This is why these reactions are used to identify the drugs of the phenothiazine series.

The sulphur atom is the most reactive in a molecule of phenothiazine and its derivatives. It can become oxidized to S^{4+} and S^{6+} .

The oxidation of phenothiazine or its derivatives with bromine in acetic acid or with another oxidizing agent such as hydrogen peroxide results in the formation of S-oxide (I) and dioxide—sulphone (II):

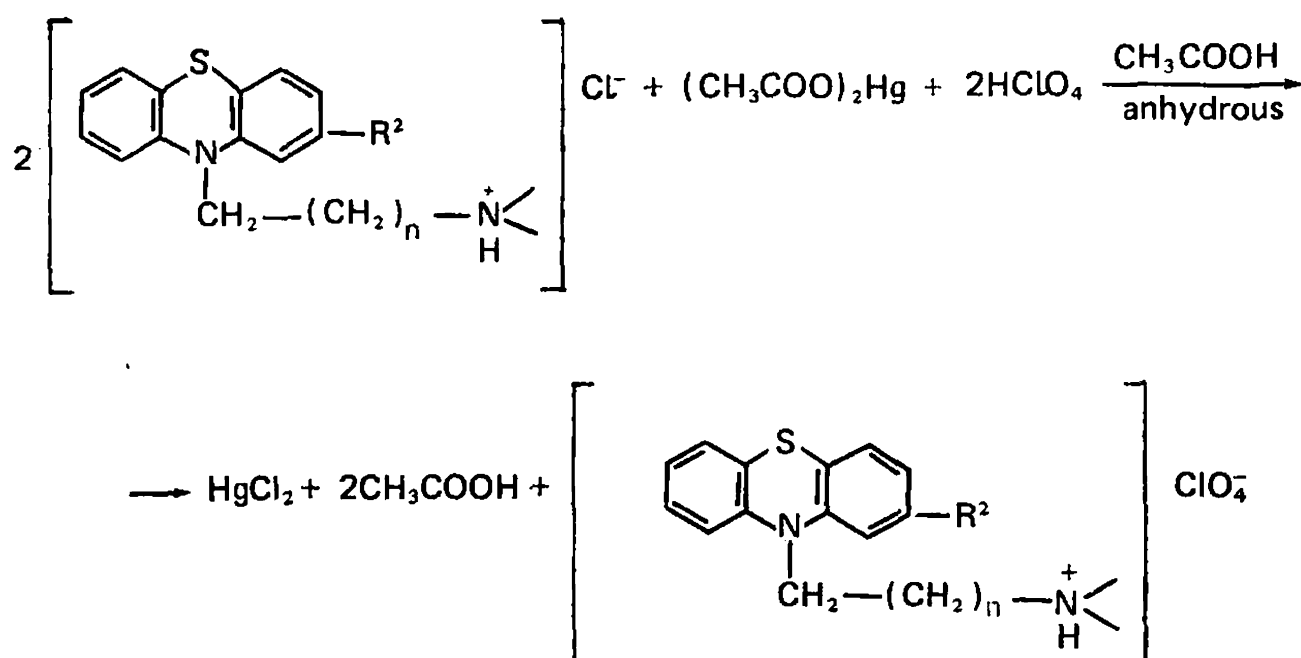


Phenothiazine derivatives can enter into a reaction with common alkaloid reagents because of the tertiary nitrogen in their molecule (see Chap. 28).

All the drugs of the phenothiazine series are employed in the form of hydrochlorides, therefore after isolation of the base with an alkali, the chloride ion is detected in the filtrate by a reaction with silver nitrate.

Among possible impurities in the drugs, the State Pharmacopoeia tolerates sulphates, heavy metals, and phenothiazine within the established limits. An acidity limit is also stipulated.

The methods used for the quantitative determination of the drugs of the phenothiazine series are quite diverse and are based on the properties of the relevant compounds. Acid-base titration in non-aqueous media is the official method. A drug is dissolved in glacial acetic acid or acetone, mercury(II) acetate is added, and the mixture is titrated with perchloric acid using a crystalline violet or methyl orange indicator:



The conventional method of neutralization with differentiating solvents is also an official one. It is recommended for a solution and

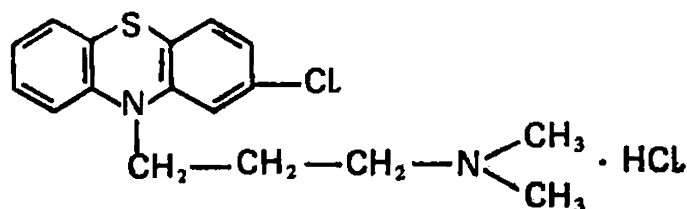
tablets of diprazine (promethazine). It is recommended to determine nitrogen by the Kjeldal method for the quantitative determination of aminazine (chlorpromazine) in a solution. Since the derivatives of phenothiazine darken in the light owing to their oxidation and are hygroscopic, they should be stored in orange glass jars tightly closed with stoppers sealed with wax in a dry place.

When working with phenothiazine derivatives, take care to prevent a powder or solution from getting onto the skin and mucous membranes because they cause great irritation, oedema of the eyelid skin, and lowering of the blood pressure. The drugs are listed in Group B.

The pharmacopoeial drugs of the phenothiazine series include aminazine (chlorpromazine), diprazine (promethazine), triftazine (trifluoperazine), and chloracyzine.

Aminazine (*Aminazinum*)

2-Chloro-10-(3-dimethylaminopropyl)-phenothiazine hydrochloride

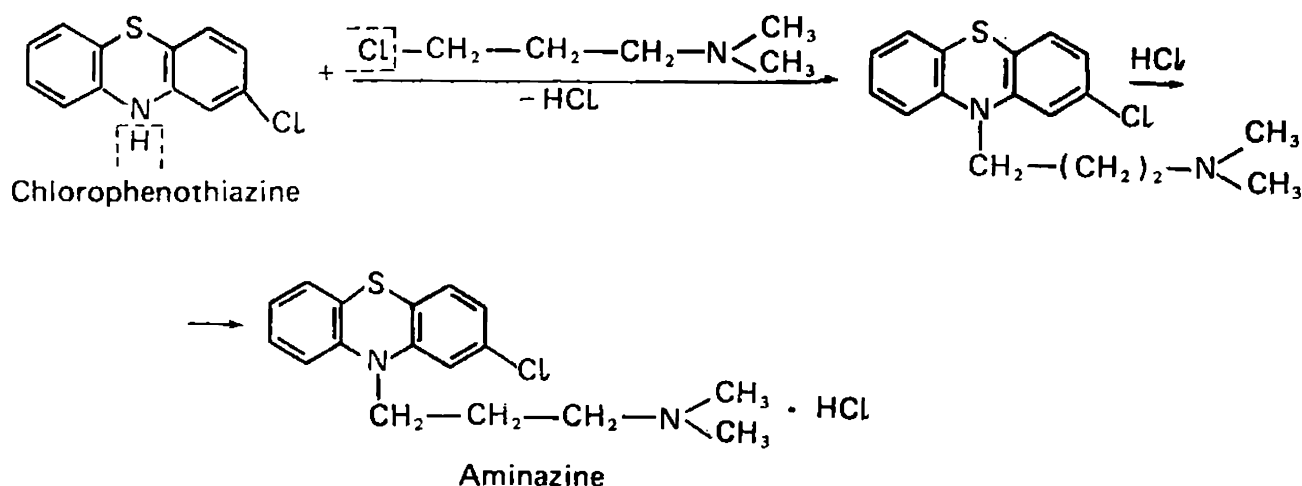


$C_{17}H_{19}ClN_2S \cdot HCl$

M.m. 355.3

This drug was first synthesized in France and named chlorpromazine. Later its synthesis was developed in the USSR. The Soviet drug was named aminazine.

The starting substance for the synthesis of aminazine is 2-chlorophenothiazine, which is condensed with 3-dimethylaminochloropropane hydrochloride in the presence of an alkali. Next, a reaction with an alcohol solution of hydrogen chloride yields aminazine:



Aminazine is a white finely crystalline powder, sometimes with a slightly creamish tint. It is slightly hygroscopic. It darkens in the light. The drug dissolves readily in water, 95% alcohol and chloroform, and is insoluble in ether and benzene.

The drug is identified:

(1) by a reaction with oxidizing agents: (a) when heated with bromine water, a transparent crimson solution forms; (b) with concentrated nitric acid, a solution of the drug becomes red, and a white suspension forms. With the subsequent addition of nitric acid, the solution becomes transparent and colourless;

(2) after the isolation of the aminazine base by the action of an alkali, Cl^- is determined in the filtrate with a silver nitrate solution.

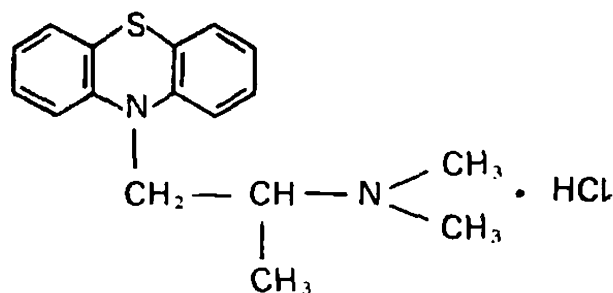
The content of aminazine in the drug is determined by acid-base titration in non-aqueous media (State Pharmacopoeia).

Aminazine is widely used in medicine, namely, in psychiatry, neurology, and surgery for amplifying the action of analgesics and local anaesthetics. A feature of aminazine is its ability to lower a body's temperature, which is of significance in the artificial cooling of an organism (hypothermia).

It is dispensed in 0.025-, 0.05-, and 0.1-g spherical tablets and in ampoules containing 2 ml of a 2.5% solution for injections.

Diprazine (*Diprazinum*)

10-(2-Dimethylaminopropyl)-phenothiazine hydrochloride

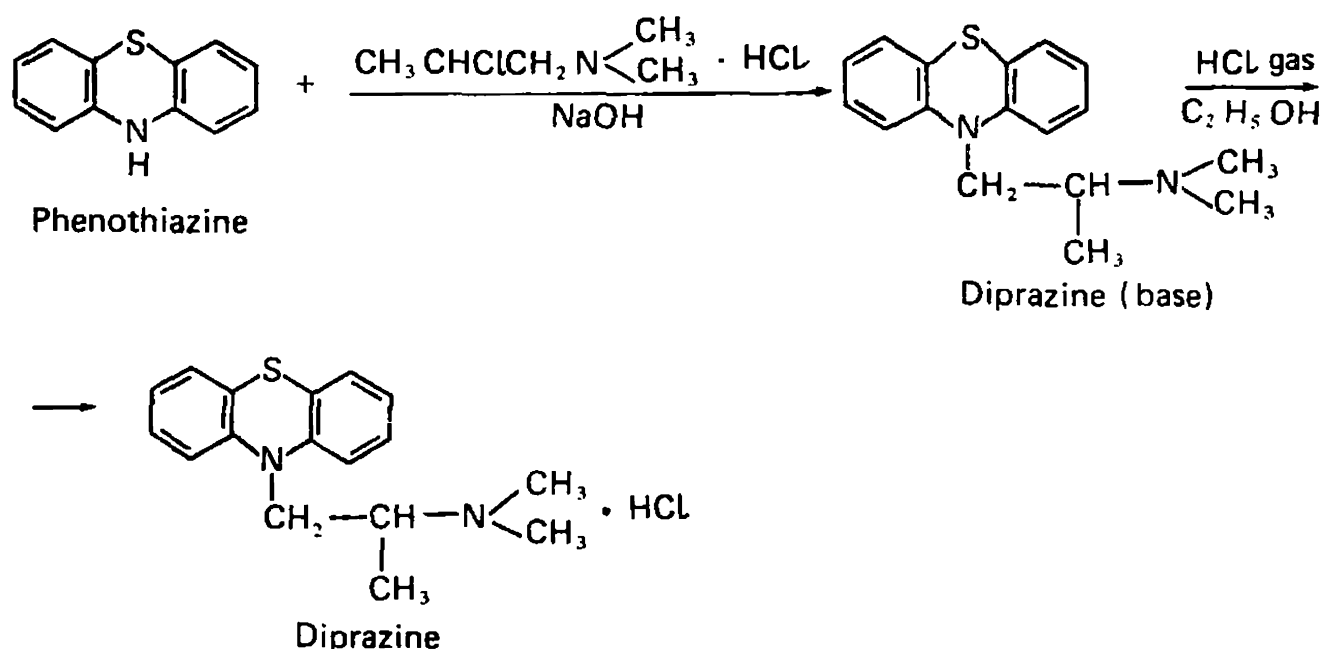


$\text{C}_{17}\text{H}_{20}\text{N}_2\text{S} \cdot \text{HCl}$

M.m. 320.89

To produce diprazine (promethazine hydrochloride), phenothiazine is condensed with the hydrochloride of 1-dimethylamino-2-chloropropane in the presence of an alkali. The obtained diprazine base is transformed by an alcohol solution of hydrogen chloride into

the hydrochloride (diprazine):



Diprazine is a white crystalline powder that dissolves readily in water, 95% alcohol and chloroform, and is insoluble in ether. The drug is identified:

(1) by a reaction with oxidizing agents, namely, (a) when heated with dilute nitric acid, the solution acquires a stable red colour; and (b) when heated with bromine water, a turbid dark crimson solution with a suspended precipitate appears;

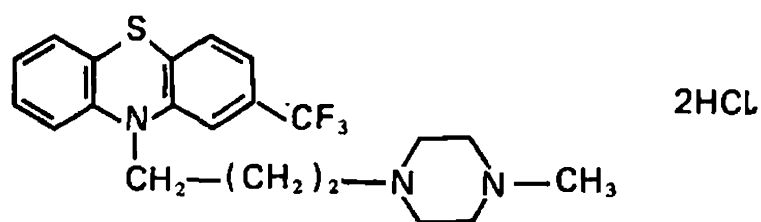
(2) after precipitation of the diprazine base with an alkali, the chloride ion in the filtrate is determined with a silver nitrate solution.

The content of diprazine in the drug is determined like that of aminazine.

It is administered in allergic diseases. It is dispensed in 0.025-g powders or coated tablets and in ampoules containing 2 ml of a 2.5% solution for injections.

Triftazine (*Triphthazinum*)

*2-Trifluoromethyl-10-[3'-(1"-methylpiperazine-4"-yl)propyl]pheno-
thiazine dihydrochloride*

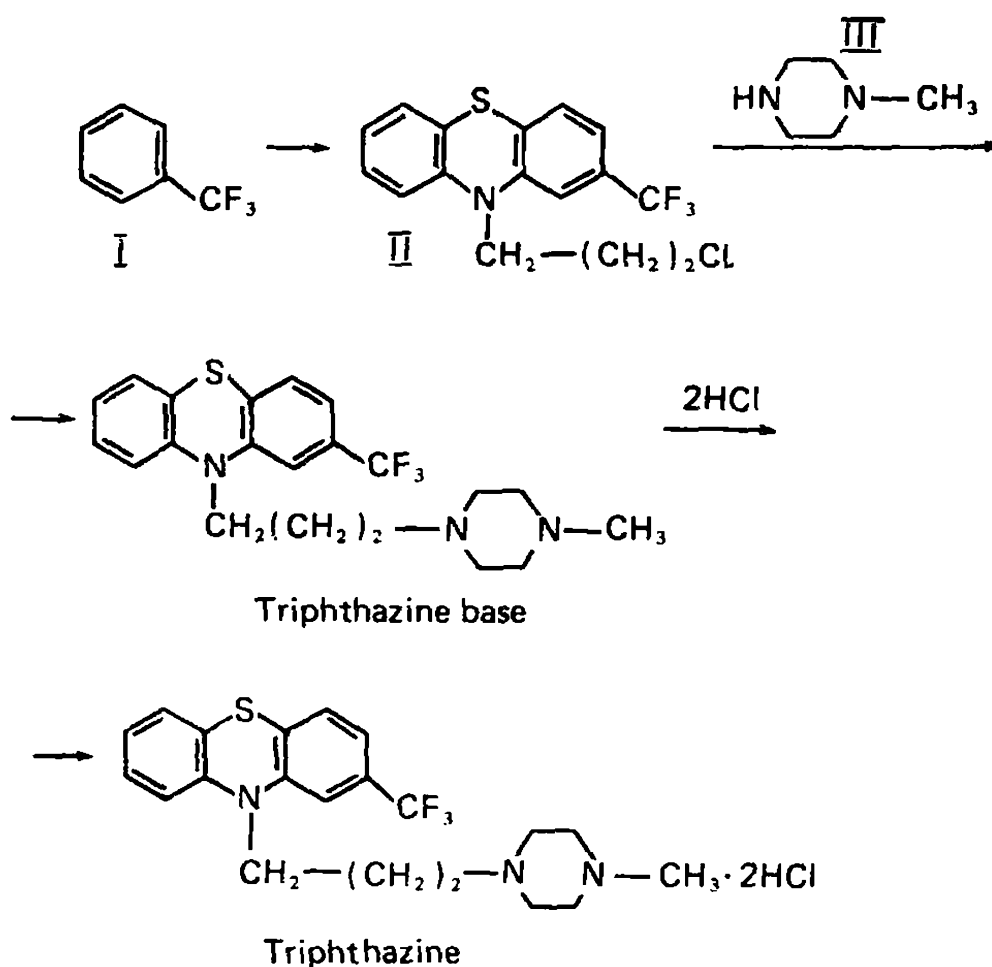


$\text{C}_{21}\text{H}_{24}\text{F}_3\text{N}_3\text{S} \cdot 2\text{HCl}$

M.m. 480.4

Triftazine was first synthesized in the USSR. Its foreign-made analogue is trifluoperazine hydrochloride. The starting substance is benzotrifluoride (I), which in a number of steps is transformed into

2-trifluoromethyl-10-chloropropylphenothiazine (II). The latter is condensed with 1-methylpiperazine (III) and the triptazine base is obtained. It is transformed into the dihydrochloride by the action of an alcohol solution of hydrogen chloride:



Triptazine (triphthazine) is a white or greenish-yellowish crystalline powder without an odour. It dissolves readily in water, is soluble in 95% alcohol, and is insoluble in ether and benzene.

The drug is identified (a) by a reaction with bromine water with heating; first the solution turns brown, and then pale pink;

(b) by a reaction with a solution of picric acid; a yellow precipitate of triptazine picrate forms (a salt formed owing to the basic properties of the tertiary nitrogen). After being washed with alcohol and dried, the triptazine picrate precipitate has a decomposition temperature of 240-243 °C;

(c) after isolation of the triptazine base with an alkali, the chloride ion in the filtrate is detected with a silver nitrate solution.

The content of triptazine in the drug is determined like that of aminazine.

Triptazine is one of the most active neuroleptic agents. It is employed in psychiatry. It suppresses nausea and vomiting. It is prescribed for oral and intramuscular administration. It is dispensed in 0.001-, 0.005-, and 0.01-g powders and coated tablets, and in ampoules containing 1 ml of a 0.2% solution.

REVIEW QUESTIONS

- Pyrazole derivatives.** 1. What is pyrazole from the chemical viewpoint?
 2. What are the properties of the hydrogen at the nitrogen in position 2 in pyrazole?
 3. Why can pyrazole be hydrogenated?
 4. Why can pyrazole derivatives be oxidized?
 5. Why are reactions of antipyrine (phenazone) with the common alkaloid reagents possible?
 6. What is the quantitative determination of antipyrine based on?
 7. For what purpose is sodium acetate added in the quantitative determination of antipyrine?
 8. What chemical properties of antipyrine must be taken into consideration when preparing medicinal forms?
 9. What reaction do aqueous solutions of amidopyrine (aminophenazone) have and why?
 10. What properties underlie the reactions of identification of amidopyrine?
 11. What is the essence of the quantitative determination of amidopyrine?
 12. How can analgin (novaminsulphon) be distinguished from antipyrine (phenazone) and amidopyrine (aminophenazone)?
 13. Compare the pharmacological action of antipyrine, amidopyrine, and analgin proceeding from the chemical structure of these substances.
 14. What are the chemical properties of butadion (phenylbutazone)?
 15. What are the acidic properties of butadion due to?
 16. What are the basic properties of butadion due to?
 17. Why is butadion readily oxidized?
 18. What properties of butadion are used in its quantitative determination?
 19. Why must butadion be protected from the action of light?
- Pyridine derivatives.** 1. What is the nature of the nitrogen in the pyridine ring?
 2. Explain how cordiamin (nikethamide) and the diethylamide of nicotinic acid form complexes with copper salts.
 3. How can the presence of tertiary nitrogen in the pyridine ring be confirmed?
- Quinoline derivatives.** 1. How can the formation of a coloured product be explained in the reaction of quinosol with iron(III) chloride?
 2. Why does chloroform have to be added in the quantitative determination of quinosol by neutralization?
 3. What properties of nitroxoline (5-NOK) is its quantitative determination based on?
- Phenothiazine derivatives.** 1. Why can the phenothiazine nucleus be considered as a dibenzoderivative of thiazine?
 2. What explains the reactivity of phenothiazine?
 3. Why can the derivatives of phenothiazine enter into a reaction with the common alkaloid reagents?
 4. Why must care be taken when working with phenothiazine derivatives?

PRACTICAL LESSON

Analysis of a 30% Solution of Antipyrine (Phenazone)

1. Perform an identification reaction:
 - (a) to several drops of the drug solution add one drop of an iron(III) chloride solution; a red colour appears;
 - (b) to several drops of the drug solution add one drop of a sodium nitrite solution and one drop of dilute sulphuric acid; an emerald green colour appears. Write the equations of the chemical reactions.

2. Conduct a quantitative determination (the iodimetric method). Transfer 5 ml of a solution of the drug into a flask for titration, add 0.3 g of sodium acetate and 10 ml of a 0.1 *N* iodine solution (from a burette). In five minutes, add 2 ml of chloroform to the mixture and agitate it until the precipitate dissolves completely. Titrate the excess iodine with a 0.1 *N* sodium thiosulphate solution until the colour disappears. Write the equations of the chemical reactions.

3. The content of antipyrine in the solution in per cent is evaluated by formula (1.1) after introducing formula (1.4) into it:

$$X = \frac{(V_0 K_0 - VK) T}{a} \times 100 = \frac{(10.00 \times K_0 - VK) \times 0.00941}{5.0} \times 100$$

where V_0 is the volume of the 0.1 *N* iodine solution, ml, V is the volume of the 0.1 *N* sodium thiosulphate solution, ml, K_0 is the correction factor for the standard iodine solution, K is the same for the standard sodium thiosulphate solution, $T = 0.00941$ g/ml, and a is the volume of the drug taken for the determination, ml.

4. Arrive at a conclusion on the content of antipyrine in the solution.

5. Are other methods possible for the quantitative determination of antipyrine?

Analysis of Amidopyrine (Aminophenazone)

1. Dissolve 0.05 g of the drug in 5 ml of water and perform two identification reactions:

(a) to 2 ml of the solution add two or three drops of an iron(III) chloride solution; a blue colour appears that rapidly vanishes, and then a brown curdy precipitate forms. After the mixture is acidified with hydrochloric acid, a blue-violet colour appears;

(b) to 1 ml of the solution add one or two drops of a silver nitrate solution; a blue-violet colour appears, and then a gray precipitate.

Write the equations of the chemical reactions.

2. Conduct a quantitative determination (by neutralization). Dissolve a sample weighing 0.05 g in 5 ml of hot water, cool it, add two drops of methyl orange and one drop of methylene blue, and titrate with a 0.1 *N* hydrochloric acid solution until the colour turns violet. Write the equation of the chemical reaction.

3. Calculate the content of amidopyrine in the preparation in per cent by formula (1.1):

$$X = \frac{VKT}{a} \times 100 = \frac{VK \times 0.0231}{0.05} \times 100$$

where V is the volume of the 0.1 *N* hydrochloric acid solution, ml, $T = 0.0231$ g/ml, and a is the mass of the sample taken for the determination, g.

The State Pharmacopoeia requires that the content be at least 99.0%.

4. Compare the result with the official requirements and make the relevant conclusion.

Analysis of Analgin (Novaminsulphon)

1. Dissolve 0.05 g of the drug in 2 ml of water and perform two identification reactions:

(a) to several drops of the solution add one or two drops of dilute hydrochloric acid and one drop of an iron(III) chloride solution; a blue colour appears that turns red, and then the colour disappears;

(b) when the remaining part of the solution is heated with 1 ml of dilute hydrochloric acid, a smell of sulphur dioxide is felt, and then of formaldehyde.

Write the equations of the chemical reactions.

2. Conduct a quantitative determination (by the iodimetric method).

Put a sample of the drug with a mass of 0.05 g into a flask for titration, dissolve it in 5 ml of water, add 1 ml of a 0.1 *N* solution of hydrochloric acid and titrate drop by drop with a 0.1 *N* iodine solution. After adding each drop, agitate until a pink colour appears. Write the equations of the chemical reactions.

3. Calculate the content of analgin in the drug in per cent by formula (1.1):

$$X = \frac{VKT}{a} \times 100 = \frac{VK \times 0.01667}{0.05} \times 100$$

where *V* is the volume of the 0.1 *N* iodine solution, ml, *T* = 0.01667 g/ml, and *a* is the mass of the drug sample, g.

The State Pharmacopoeia requires that the analgin content be at least 99.0% and at most 101.0%.

4. Compare the result with the official requirements and make the relevant conclusion.

5. Proceeding from the chemical properties of analgin, propose other possible methods for the quantitative determination of it.

IV. Natural Biologically Active Compounds

Chapter 28. Alkaloids

Alkaloids are substances mostly of plant and rarely of animal origin. They are specific products of metabolism mainly of a plant cell, although recently a number of alkaloids have been isolated from microorganisms, insects, and animals.

The discovery of alkaloids and their use in medicine as drugs relates to the beginning of the 19th century, when the structure of morphine, atropine, caffeine, and quinine was established. At present, the number of known alkaloids is approaching 10 000, but more and more new representatives of this class of compounds are continuing to be discovered. And although from the time of discovery of the first alkaloids over 150 years have elapsed, the interest in them has not weakened to date. The explanation is that alkaloids have a high physiological activity and have found the most diverse applications in medicine, veterinary practice, the food industry, and agriculture.

In medicine, alkaloids are successfully used as drugs in the treatment of cardiovascular, nervous, alimentary tract, and many other diseases. It is known at present that some alkaloids are employed in the treatment of malignant neoplasms.

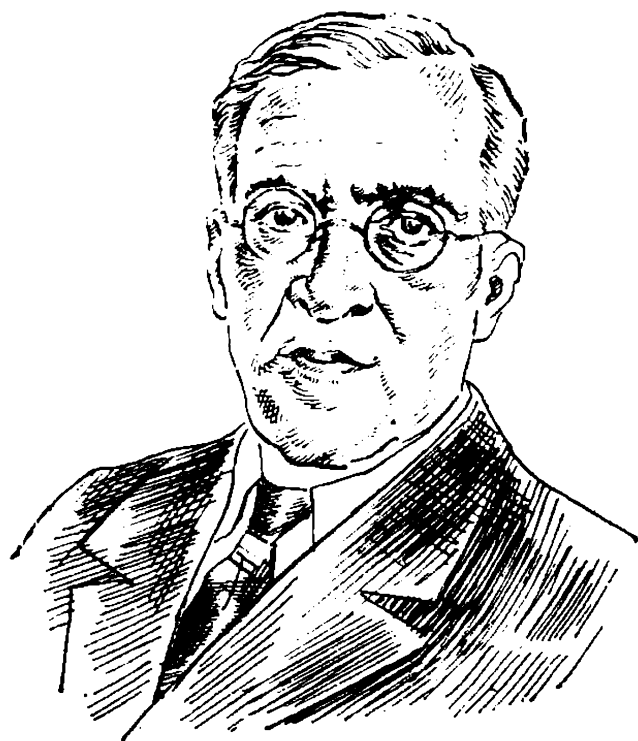
The value of alkaloids also consists in that their preparations have a rapid action, which is especially important in cardiovascular diseases and spastic phenomena. Moreover, they have no cumulative properties. The importance of alkaloids for the life of mankind was determined very concisely and figuratively by the Russian scientist E. Shatsky: "Alkaloids have the same significance for medicine as the discovery of iron for the world's progress."

Plants generally contain a mixture of alkaloids with a similar chemical structure in the form of salts of organic acids, most frequently of malic, citric, and oxalic acids. Some alkaloids are found in a plant in the form of salts of specific acids. For example, the alkaloids of cinchona bark are in the form of salts of quinic acid, while morphine and its companions are in the form of salts of meconic acid.

The alkaloid content in a plant is very low. In most cases, it is tenths of a per cent, and only very rarely does the content of all the alkaloids reach 10-15% (the alkaloids of opium).

The priority in the discovery of many alkaloids belongs to Russian scientists. A. Voskresensky discovered the alkaloid theobromine in cocoa seeds. F. Gizé made the assumption that cinchona bark contains cinchonine, which was later established to be quinine.

We must not fail to mention the outstanding Russian chemist, Academician A. Orekhov, who was the first in 1928 to start studying the country's plants for their alkaloid content.



A. Orekhov (1881-1939)

The works of Orekhov and his school in alkaloid chemistry made the USSR the leading country in the world in this field, therefore Orekhov is by right considered to be the founder of the chemistry of alkaloids in the USSR.

The first alkaloid discovered in the USSR, anabasine, was isolated from the Central Asian plant *Anabasis aphylla*.

The studying of alkaloid-bearing plants resulted in the creation of the drug securinine having an action like that of strychnine. A major achievement in the last few decades was the complete

chemical synthesis of such complex alkaloids as morphine, strychnine, reserpine, and emetine.

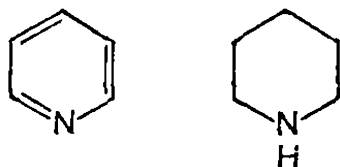
As regards their physical properties, almost all the alkaloids are solid crystalline colourless and odourless substances with a bitter taste. The overwhelming majority of them are optically active.

From the chemical standpoint, the alkaloids are organic substances of a basic nature because their molecules always contain nitrogen. The alkaloids are chiefly tertiary amines, and only some of them are secondary amines or derivatives of tetrasubstituted ammonium bases. Alkaloids can be considered as ammonia derivatives in which the hydrogen atoms have been replaced by radicals. Like ammonia, the alkaloids produce salts with acids (of the type of ammonium salts). In addition to nitrogen, alkaloids sometimes contain oxygen in their molecule. The latter may be in the form of the alcohol or phenol hydroxyl group, a carbonyl, ether, or ester group.

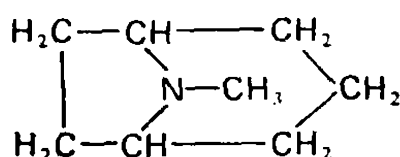
The alkaloids have the most varied chemical structure. They can be compounds with one or more carbocyclic, heterocyclic, and open carbon chains.

Classification. A chemical classification has been adopted for alkaloids that is based on the nature of the carbon-nitrogen nucleus of the alkaloid molecule, for example:

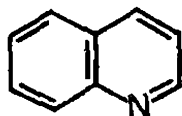
(1) pyridine and piperidine derivatives (lobeline and its companions):



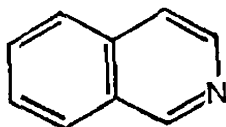
(2) tropane derivatives (atropine, hyoscyamine, scopolamine, cocaine):



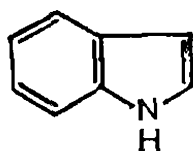
(3) quinoline derivatives (quinine, quinidine, cinchonine):



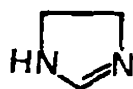
(4) isoquinoline derivatives (opium alkaloids):



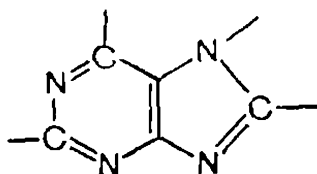
(5) indole derivatives (physostigmine, strychnine, reserpine):



(6) imidazole derivatives (pilocarpine):



(7) purine derivatives (caffeine, theobromine, theophylline):



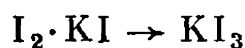
Detection reactions. Alkaloids are detected with the aid of group reactions typical of a whole group of alkaloids, and specific reactions

for an individual alkaloid due to its chemical properties and structure and the presence of functional groups.

The group reactions are based on the ability of the alkaloids to yield simple or complex salts with various acids, heavy metal salts, complex iodides, and other substances. The products of the reactions of these reagents with alkaloids are generally insoluble in water, therefore these reactions are called **precipitation reactions**, and the reagents—**precipitants**.

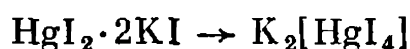
Among the group alkaloid precipitants, the following are used most frequently:

(1) a solution of iodine in potassium iodide (Bouchardat's, Wagner's, or Lugol's reagent):



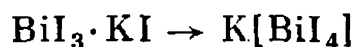
With acidified aqueous solutions of alkaloid salts, it yields brown precipitates. Bouchardat's, Wagner's, and Lugol's reagents differ only in the concentration of the iodine and potassium iodide;

(2) a solution of mercury iodide in potassium iodide (Mayer's reagent):



With most acidified or neutral alkaloid solutions, it yields white or slightly yellowish precipitates; it precipitates almost all the alkaloids except for caffeine and colchicine;

(3) a solution of bismuth iodide in potassium iodide (Dragendorff's reagent):



With solutions of alkaloid sulphates and chlorides, it yields orange-red or reddish-brown amorphous and more rarely crystalline precipitates;

(4) phosphomolybdic acid (Sonnenschein's reagent):



This reagent is one of the most sensitive for alkaloids; it produces yellowish amorphous precipitates that after some time acquire a blue and green colour because of the reduction of the molybdic acid;

(5) phosphotungstic acid (Scheibler's reagent):



The reagent forms amorphous white precipitates with almost all the alkaloids;

(6) a freshly prepared 10% aqueous tannin solution with a 10% alcohol solution. It forms white or yellow precipitates with alkaloid salts in a neutral and weakly acidic medium;

(7) picric acid (a 1% aqueous solution). It precipitates yellow

let $2k$ be the number of nodes of odd degree in t . Then the number β of different decompositions of t into k edge-disjoint paths is given by

$$\beta = \prod_{i=1}^{n-1} f(i)^{n_i}, \quad (5.14)$$

where $f(2i-1) = f(2i) = 1 \cdot 3 \cdot 5 \cdot \dots \cdot (2i-1)$.

Proof. For a set R , let $\alpha(R)$ denote the number of its elements. Let S_u , $u=1, 2, \dots, n$, be the set consisting of all the edges of t incident at the node u . Partition the elements of S_u into a set R_u of disjoint subsets r_{ux} with the following property: Let $R_u = \{r_{ux}\}$. If $\alpha(S_u)$ is even, then $\alpha(r_{ux})=2$ for all x ; and if $\alpha(S_u)$ is odd, then $\alpha(r_{u1})=1$ and $\alpha(r_{ux})=2$ for $x \geq 2$. It is not difficult to see that if the node u is of degree i then there are $f(i)$ different partitions of the elements of S_u into R_u .

Consider a system $\mathcal{R} = \{R_1, R_2, \dots, R_n\}$ of partitions with the above property. In the following, we shall show that for each choice of $\mathcal{R}$ there corresponds a unique decomposition of t into k edge-disjoint paths, and vice versa. The dissection process amounts to repeatedly generating a path according to $\mathcal{R}$ and then removing it. The rules for generating a path according to $\mathcal{R}$ are outlined as follows:

(1) We start at a node w of odd degree and then proceed along the edge contained in r_{w1} of R_w .

(2) If we arrive at an edge (u, v) in r_{vx} of R_v , then for $x \neq 1$ we proceed along the other edge contained in r_{vx} , and for $x=1$ a path is constructed.

It is evident that the above procedure will decompose t into k edge-disjoint paths. Conversely, to each decomposition there corresponds a system of partitions with the above property. It follows that the number β of different decompositions is equal to the number of different systems $\mathcal{R}$ with the required property. Thus, we have

$$\beta = \prod_{x=1}^n f(d(x)) = \prod_{i=1}^{n-1} f(i)^{n_i}, \quad (5.15)$$

which completes the proof of the theorem.

As an illustration, consider the tree t as shown in fig. 5.2. We have $n_1=4$, $n_2=4$, $n_3=2$, and $n_i=0$ for $i=4, 5, \dots, 9$. Since there are six nodes of odd degree in t , i.e., $k=3$, it follows that any decomposition of t into edge-disjoint paths contains at least 3 paths, and in fact there are

$$\beta = (1)^4 (1)^4 (3)^2 = 9$$

different decompositions possible for t . They are given by

$$\begin{aligned} &\{e_1e_2, e_3e_5e_4, e_6e_7e_8e_9\}, \{e_1e_2, e_3e_6e_7e_8e_9, e_5e_4\}, \{e_1, e_2e_3e_5e_4, e_6e_7e_8e_9\}, \\ &\{e_1, e_2e_3e_6e_7e_8e_9, e_5e_4\}, \{e_2, e_1e_3e_5e_4, e_6e_7e_8e_9\}, \{e_2, e_1e_3e_6e_7e_8e_9, e_5e_4\}, \\ &\{e_1e_3, e_2, e_4e_5e_6e_7e_8e_9\}, \{e_2e_3, e_1, e_4e_5e_6e_7e_8e_9\}, \{e_3, e_1e_2, e_4e_5e_6e_7e_8e_9\}. \end{aligned}$$

§ 4. The Wang-algebra formulation

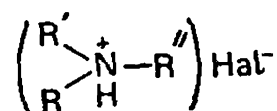
In many engineering applications of graph theory, it is necessary that we list all the trees and cotrees of a graph. For example, the topological formulas for network functions are stated in terms of tree or cotree products. Thus, the efficiency with which a complex linear system can be analyzed by a digital computer using topological formulas as a tool depends largely upon the efficiency with which the trees or cotrees of the associated graph are generated.

The simplest way to generate trees of an n -node connected graph is to examine all possible combinations of $n-1$ edges. If b is the total number of its edges, we must examine $\binom{b}{n-1}$ sets. For a moderately large graph, the number of these sets is too large even for a high-speed digital computer. For example, for a graph with 20 nodes and 40 edges the number of such sets to be examined is 137846528820.

The main difficulties in generating trees by direct approach lie in the fact that the number of operations increases exponentially with the number of nodes. What is needed is a method of generating all trees which requires that the number of operations vary approximately linearly with the number of nodes of the graph, and which does not need to check every new generated tree against all the previously found ones in order to eliminate duplications, because the exhaustive checking procedure is an extremely time-consuming process as the number of trees, as the above example shows, could be in the *millions*. Apart from slowing down the process, this fact also limits the sizes of the systems that can be analyzed by a digital computer, since one must retain the set of all trees in computer memory and check each new tree against the list for possible duplications.

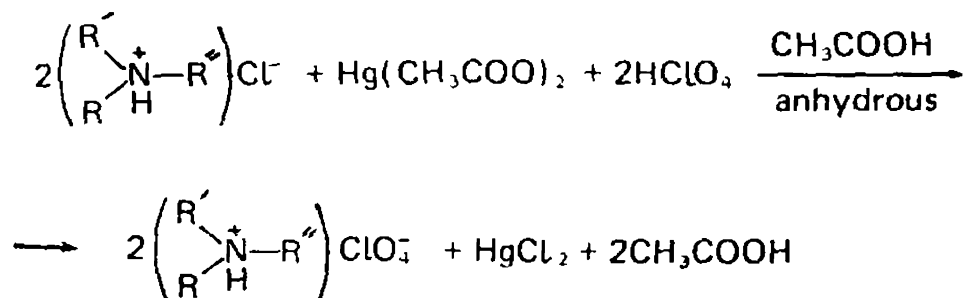
In this section, we shall demonstrate the intimate relationships among trees, cotrees, multi-trees, multi-cotrees, circuits, paths, and cuts, and then show how these relationships can be used to generate trees and cotrees. The entire section is based on the recent work of CHEN and MARK [1969], BERGER and NATHAN [1968], and CHEN [1969d-h, 1971c].

At present, acid-base titration in non-aqueous media has been adopted as the official method for the quantitative determination of alkaloids, both bases and salts. Alkaloid preparations are more frequently used in medicine in the form of salts of the hydrohalic acids (HCl, HBr, HI):



They are determined according to the base, and not the acid residue. In this case, glacial or anhydrous acetic acid is used as the non-aqueous solvent, perchloric acid as the titrant, and crystal violet as the indicator.

To eliminate the influence of the halide ion on the titration process, mercury(II) acetate $Hg(CH_3COO)_2$ is added. It transforms the halide ion into a virtually non-dissociating compound mercury(II) halide $Hg(Hal)_2$. The non-aqueous titration of the alkaloid salt proceeds according to the reaction:

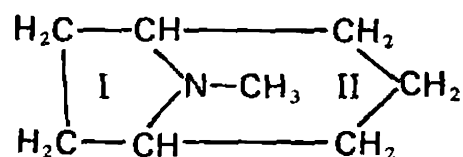


Some alkaloids can be determined quantitatively by precipitation using a variety of precipitants such as silver nitrate and iodine. For example, before the method of non-aqueous titration was included in the State Pharmacopoeia, caffeine was determined iodimetrically. It was precipitated by an iodine solution in the form of a periodide insoluble in water; the excess iodine was titrated with sodium thio-sulphate. This method is recommended by the State Pharmacopoeia for the quantitative determination of caffeine salts, for example of sodium caffeine benzoate.

Lately, physicochemical methods of determining alkaloids (photo-metric, chromatographic, etc.) have been introduced.

28.1. TROPANE DERIVATIVES

The parent of this alkaloid group is tropane. It is a bicyclic system consisting of two heterocyclic rings, namely, a five-membered pyrrolidine ring (I) and a six-membered piperidine ring (II):

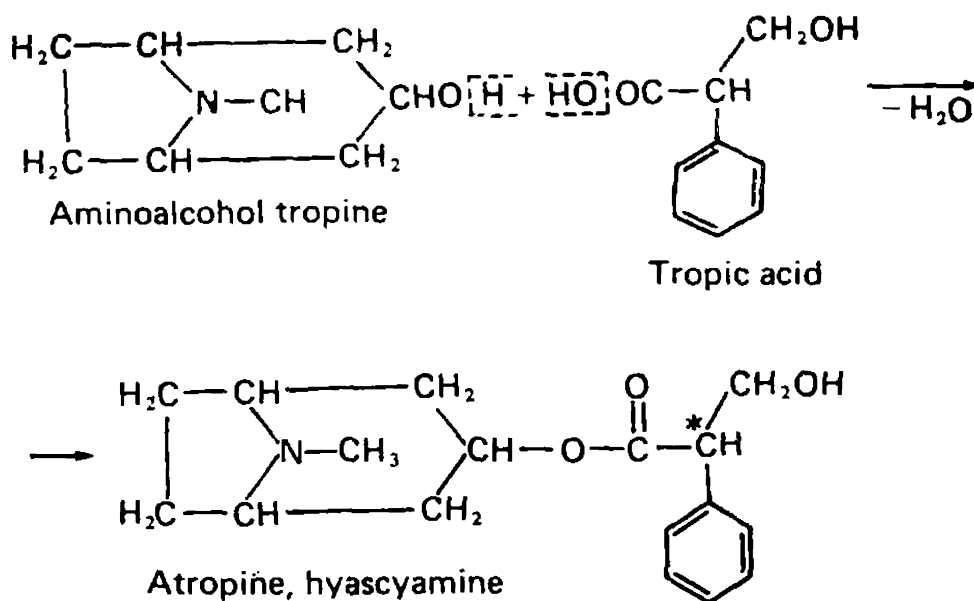


The main representatives of the tropane alkaloids are racemic atropine and its levorotatory isomer hyoscyamine, scopolamine, cocaine and its companions—truxillines and cinnamylcocaine.

Atropine. Atropine and its levorotatory isomer hyoscyamine are found in plants of the nightshade (*Solanaceae*) family, namely, deadly nightshade (*belladonna*), datura, henbane, and various species of duboisin. But these plants contain only traces of atropine. The main form in which an alkaloid appears in plants is hyoscyamine.

Atropine is formed from hyoscyamine in the process of separating alkaloids from plants: a water extract from the leaves and roots of deadly nightshade freed of ballast substances is treated with soda or a nitric acid solution. Bases of the alkaloids precipitate and are extracted with chloroform. The obtained extract of alkaloid bases is evaporated at 114-116 °C. Under these conditions, the levorotatory hyoscyamine transforms into the racemate—atropine.

Hyoscyamine and atropine have the same chemical structure and are esters of tropine (an alcohol) and tropic acid:



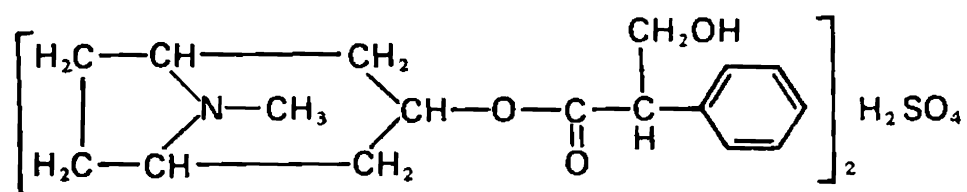
The optical activity of the alkaloid is due to the asymmetric carbon atom of the tropic acid, which produces two optical isomers (d and l) and a racemate (dl).

Atropine is formed by the racemic (inactive) tropic acid, and hyoscyamine by its levorotatory isomer. The structure of the atropine molecule was established in 1901, and only 16 years later was it synthesized, which confirmed its structure. The presence of tertiary nitrogen in the atropine molecule explains its basic properties. As a base, it reacts with acids to form soluble salts.

Atropine sulphate is a pharmacopoeial preparation.

Atropine Sulphate (*Atropini sulfas*)

d,l-Tropic acid tropine ester sulphate



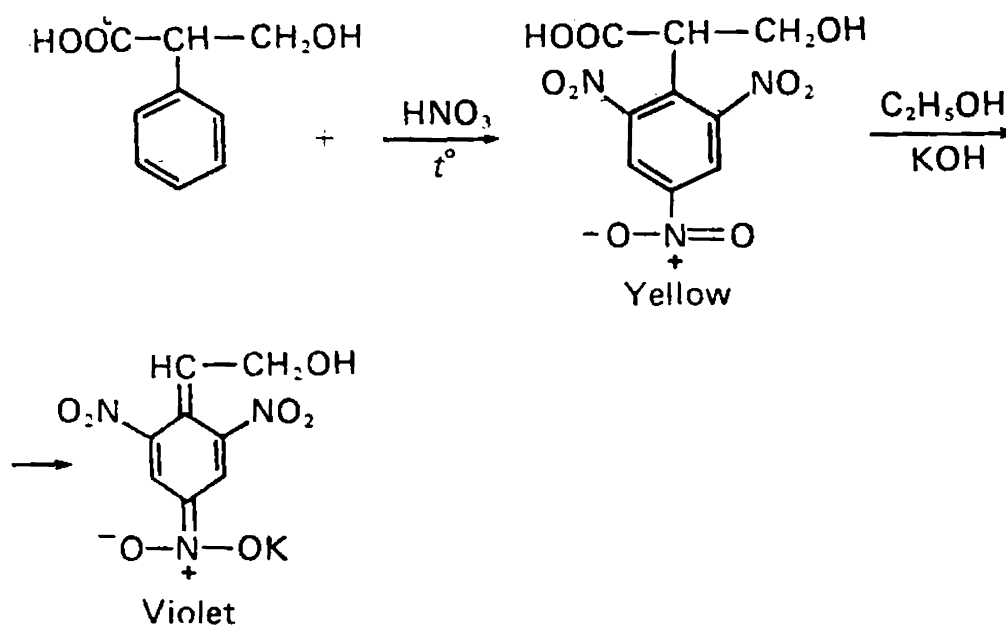
$(\text{C}_{17}\text{H}_{23}\text{NO}_3)_2 \cdot \text{H}_2\text{SO}_4 \cdot \text{H}_2\text{O}$

M.m. 694.8

Atropine sulphate is a white crystalline or granular powder without an odour. It dissolves readily in water and alcohol, and does not dissolve in chloroform and ether. The drug is identified by:

(a) the formation of a white precipitate when a barium chloride solution is added; the precipitate does not dissolve in acids and alkalies (SO_4^{2-});

(b) Vitali's reaction (for tropic acid); atropine is heated with concentrated nitric acid and is evaporated; a yellow polynitro compound forms; when an alcohol solution of an alkali (KOH) is added, a violet colour appears:



(c) the melting point (115-117 °C) of the atropine base after its precipitation by an ammonia solution and drying. These reactions are official.

Atropine gives precipitation reactions with group I alkaloid reagents, the most specific of which is picric acid with which atropine forms yellow picrates. This reaction is used in the quantitative determination of an atropine solution (*Solutio Atropini sulfatis 0.1% pro injectionibus*) by the photolorimetric method.

The quality of the drug is determined by establishing the acidity limit because there may be an excess acidity when producing atropine

sulphate. An admixture of apo-atropine (atropine anhydride) may be present in atropine if the temperature regime was violated in the extraction of the alkaloids from the plants (above 116 °C). To detect this admixture, a nitric acid solution is added; the apo-atropine does not dissolve in it and precipitates. Since the State Pharmacopoeia does not tolerate this admixture in the drug, no turbidity should appear immediately after a nitric acid solution is added to a solution of the drug.

The drug may contain various organic impurities that are detected by the action of concentrated sulphuric acid: resinification occurs owing to which the solution becomes brown.

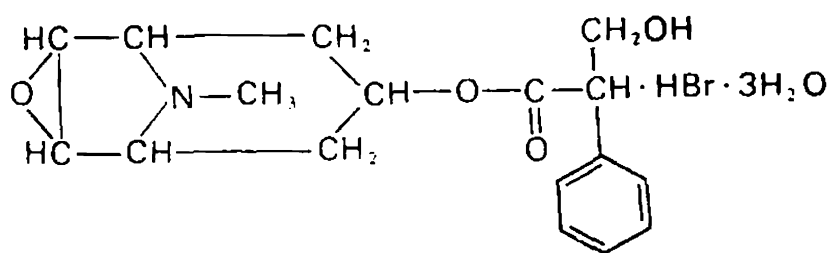
The official method for determining the content of atropine sulphate is acid-base titration in non-aqueous media. Glacial acetic acid is the non-aqueous solvent. A weighed sample of the drug is titrated with perchloric acid using a crystal violet indicator up to a green colour of the solution.

Atropine in its pharmacological action is a cholinolytic agent, simultaneously exhibiting a spasmolytic effect. Atropine also has a mydriatic effect, i.e. can cause dilatation of the pupil. This property of atropine is widely used by ophthalmologists for studying the eye fundus. Atropine sulphate is prescribed orally and locally in the form of eye drops.

It is dispensed in a powder and in ampoules containing 1 ml of a 0.1% solution. It is listed in Group A.

A drug with a similar pharmacological action is scopolamine employed in medicine in the form of its salt with hydrobromic acid. It is a pharmacopoeial drug.

Scopolamine Hydrobromide (*Scopolamini hydrobromidum*)



$C_{17}H_{21}NO_4 \cdot HBr \cdot 3H_2O$

M.m. 438.3

Scopolamine hydrobromide forms colourless transparent crystals readily soluble in water, alcohol, and poorly in organic solvents.

The chemical structure of a scopolamine hydrobromide molecule, unlike that of atropine sulphate, includes the alcohol scopine, which is esterified by the same tropic acid. Consequently, the analysis of scopolamine is similar to that of atropine (Vitali's reaction, a reac-

tion with the group alkaloid reagents) and differs from it because Br^- is present instead of SO_4^{2-} .

The bromide ion is detected either with a silver nitrate solution, or by oxidation to elementary bromine, which colours chloroform yellow.

The presence of the drug and its purity can be determined by its melting point (192-196 °C) and specific rotation from -22° to -26° (a 5% aqueous solution prepared from the dried drug).

The admixtures in the drug are the same as in atropine (the acidity limit, the presence of apo-atropine, apo-scopolamine, and reducing substances are determined).

The content of the drug is determined by acid-base titration in non-aqueous media (State Pharmacopoeia).

Scopolamine has the same pharmacological action as atropine. It also relates to cholinolytic agents and like atropine causes dilatation of the pupil. But its mydriatic effect is shorter. Scopolamine has a considerably more pronounced action on the central nervous system. It is employed as a tranquilizer and soporific in frequent insomnia and in psychiatry.

It is dispensed in powders and in ampoules containing 1 ml of a 0.05% solution.

It should be stored in well closed orange glass jars. It is listed in Group A.

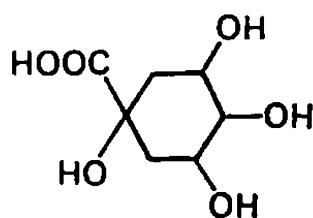
28.2. QUINOLINE DERIVATIVES

Of the natural compounds that are quinoline derivatives, the alkaloid quinine and its numerous companions are of the greatest practical value. This group of natural alkaloids is encountered in various species of the madder family *Rubiaceae*, and chiefly in the two genres *Cinchona* and *Remijia*.

Over 300 years ago, cinchona bark was used to treat tropical fever. There are many stories and legends on the discovery by Europeans of the healing effect of cinchona bark. The cinchona is a native of South America.

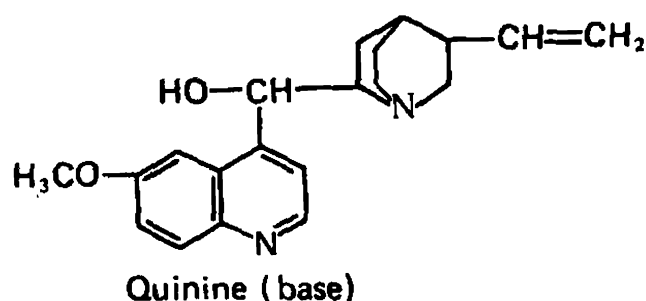
Attempts were made in the USSR to cultivate various species of cinchona first in the Far East, and then on the Black Sea shore of the Caucasus. But these attempts were not successful.

Cinchona bark contains over 20 alkaloids, of which four are the most significant, namely, quinine, quinidine, cinchonine, and cinchonidine, the main one of which is quinine. All these alkaloids are present in cinchona bark in the form of salts of quinic acid:



The alkaloid content in cinchona bark fluctuates from 2 to 15%. Although cinchona bark was known in Europe as an antipyretic back in the 17th century, its active substance—quinine was first isolated only in 1816 by professor F. Gizé of the Kharkov University. In 1820, the French pharmacists P. Pelletier and J. Caventou separated quinine together with cinchonine in the pure crystalline form.

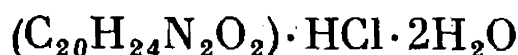
The structure of a quinine molecule is based on a nucleus of 6-methoxyquinoline that is bound by its secondary alcohol group to a quinuclidine nucleus, which is a condensed system of two piperidine rings:



The other closest analogues of quinine (quinidine, cinchonine, and cinchonidine) differ from it only in the nature of the substituent in position 6 of the quinoline nucleus (C_6) and also in optical isomerism; quinine and quinidine have a methoxy group $-OCH_3$ in position 6 of the quinoline nucleus, whereas the other two alkaloids do not have this group.

Quinine and cinchonidine are levorotatory alkaloids, while quinidine and cinchonine are dextrorotatory ones. Containing two tertiary nitrogen atoms in their molecule, quinine and its homologues have basic properties, these properties being more pronounced in the nitrogen of the quinuclidine ring. Consequently, salts form first of all owing to this nitrogen. Thus, being a ditertiary diacid base, quinine forms two kinds of salts, namely, acidic (both nitrogens are neutralized) and neutral ones (only one nitrogen is neutralized).

Quinine Hydrochloride (*Chinini hydrochloridum*)



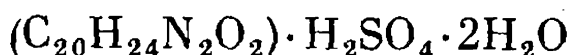
M.m. 396.92

Quinine Dihydrochloride (*Chinini dihydrochloridum*)



M.m. 397.35

Quinine Sulphate (*Chinini sulfas*)

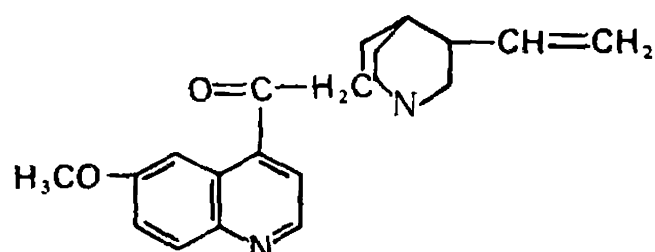


M.m. 458.52

These salts differ from one another in their physical properties, namely, their solubility, melting point, angle of rotation, and

amount of crystallization water. Of the quinine salts, the dihydrochloride dissolves the best in water, while quinine sulphate dissolves sparingly. In their appearance, the above quinine salts are colourless lustrous acicular crystals (quinine hydrochloride, quinine sulphate), colourless crystals (quinine dihydrochloride), or white crystalline powders. They have no odour and a very bitter taste.

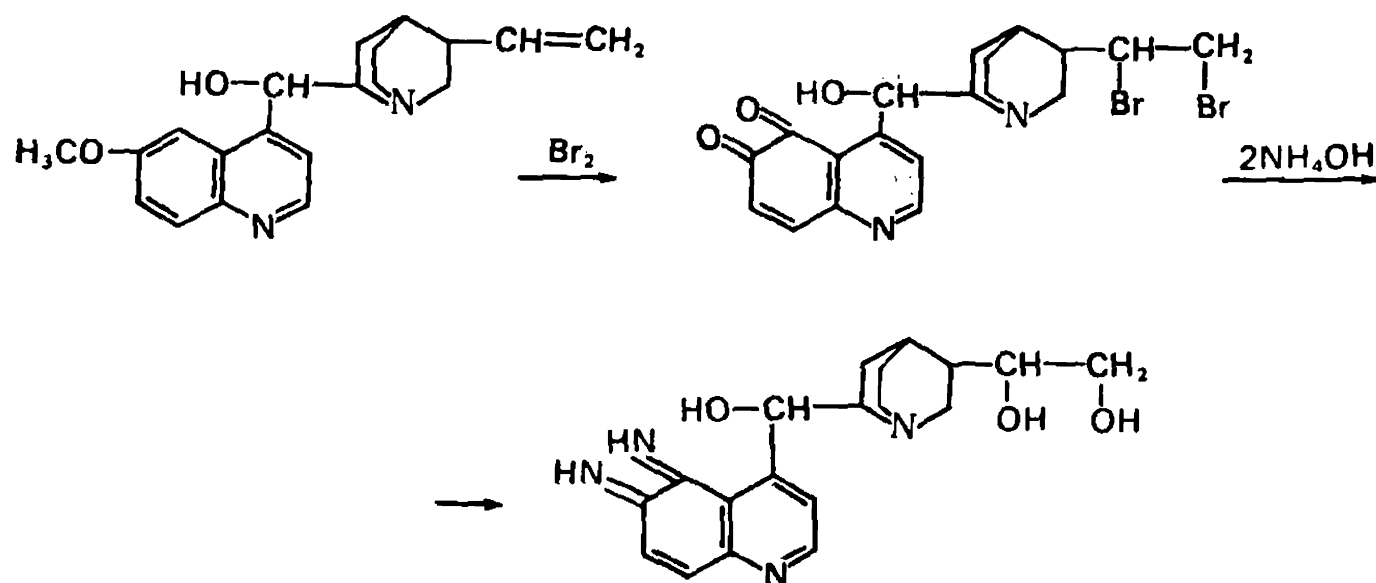
Unlike the other salts, the sulphates produce a light blue fluorescence. Salts of quinine with oxygen-containing acids (for example, quinine sulphate) when heated readily isomerize to quinotoxin—a secondary base of a ketone nature:



Quinotoxin is very toxic. To prevent its formation, quinine salts must never be sterilized with oxygen-containing acids. In this respect, hydrochlorides have an advantage over sulphates because they can easily be sterilized when heated without decomposition.

Quinine salts are identified by:

- (a) a reaction for the acid anion (SO_4^{2-} , Cl^-) forming a salt with the quinine base (a reaction distinguishing quinine salts);
- (b) the formation of thalleoquin having an emerald green colour; this reaction is a group one and specific for salts of quinine and its derivatives having a methoxy group $-\text{OCH}_3$ in position 6 of the quinoline nucleus. The preparation is oxidized with bromine water, and then an ammonia solution is added drop by drop; an emerald green colour appears, i.e. thalleoquin forms:



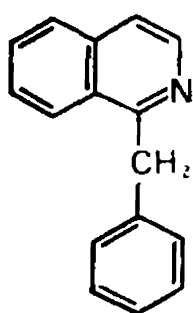
The content of quinine preparations is determined from the mass of the base after its precipitation with sodium hydroxide.

The salts are dispensed in powders and tablets, quinine dihydrochloride—in ampoules containing 2 ml of a 50% solution.

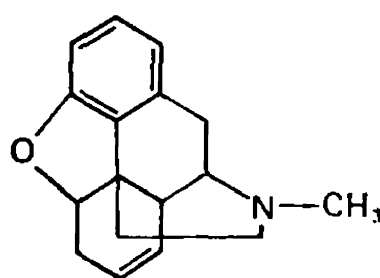
The drugs are employed to treat malaria. They should be stored in a well closed container protected from the action of light.

28.3. ISOQUINOLINE DERIVATIVES

The isoquinoline heterocycle is contained in the structure of many plant alkaloids used in medicine, of which alkaloids that are derivatives of benzyloisoquinoline (I) and phenanthreneisoquinoline (II) present the greatest interest:



I



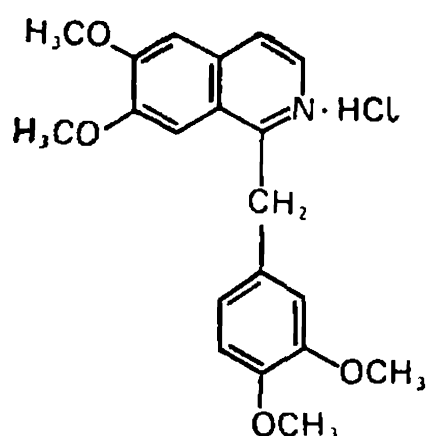
II

BENZYLISOQUINOLINE DERIVATIVES

This group of alkaloids includes papaverine and narcotine (noscapine) produced from opium. The pharmacopoeial preparation of papaverine is its salt—papaverine hydrochloride.

Papaverine Hydrochloride (*Papaverini hydrochloridum*)

1-(3,4-Dimethoxybenzyl)-6,7-dimethoxyisoquinoline hydrochloride



$C_{20}H_{21}NO_4 \cdot HCl$

M.m. 375.86

The natural source of the alkaloid papaverine is opium—a dried or partly dried latex obtained from unripe capsules of the opium poppy *Papaver somniferum* (family *Papaveraceae*).

Papaverine was isolated from opium very long ago—back in 1884. Later its structural formula was established, which was confirmed by synthesis carried out in 1910. During subsequent years, various modifications and improvements were introduced into the synthesis of papaverine to achieve the most rational and economically profitable commercial way of producing this alkaloid. At present papaverine is produced synthetically.

Papaverine hydrochloride is a white crystalline powder with a slightly bitter taste. It dissolves slowly in water, sparingly in alcohol, and is soluble in chloroform. Papaverine is a weak monoacidic base. Its salts readily hydrolyze.

Most reactions identifying papaverine are based on the oxidation of the methoxy groups in its molecule. Depending on the oxidizing agent, the oxidation products have various colours. For example, when the drug is reacted with concentrated nitric acid, a yellow colour appears that turns orange when heated in a water bath. When reacted with concentrated sulphuric acid, the oxidation products are coloured violet (State Pharmacopoeia). A reaction with bromine water forms a yellow precipitate, and with Marchi's reagent (formaldehyde + concentrated sulphuric acid) forms a red colour transforming to yellow, and then to bright orange.

In addition to the above identification reactions, the State Pharmacopoeia recommends determination of the melting point of the papaverine base recovered from the salt with sodium acetate. It should be 145-147 °C. The chloride ion is detected in the filtrate.

The content of the drug is determined by acid-base titration in non-aqueous media similar to the other halide salts of alkaloids.

Papaverine is characterized by a high spasmolytic activity. It relaxes the smooth muscles, which is of major importance in surgical operations. It is administered orally and subcutaneously in the form of 1-2% solutions.

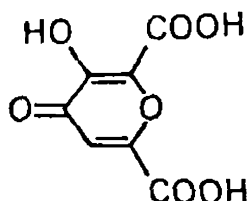
It is dispensed in 0.02-g powders and tablets.

The drug should be stored in well closed containers protected from the action of light. It is listed in Group B.

PHENANTHRENEISOQUINOLINE DERIVATIVES

The main alkaloids of this group are morphine and codeine, which together with their numerous companions are contained in opium produced from the opium poppy *Papaver Somniferum*. The alkaloids

are contained in the opium in the form of salts of meconic acid:



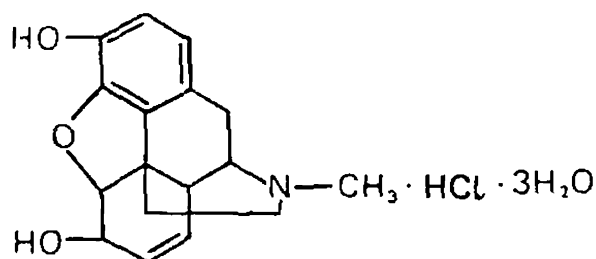
Opium has a very complex composition. In addition to 25 alkaloids, it contains carbohydrates, proteins, resins, fats, rubber-like substances and others forming the main mass of opium (75%). This is why the separation and purification of the alkaloids from all these accompanying impurities were a very involved process substantially affecting the cost of production of the alkaloids.

In this connection, searches were undertaken to find a cheaper raw material for the production of the opium alkaloids. This task was coped with successfully by a group of Soviet scientists (A. Bankovsky *et al*). Their attention was attracted to the oil-bearing poppy cultivated in large amounts in the USSR to produce poppy oil. The latter is employed not only as a food product, but also for pharmaceutical purposes, and for manufacturing the highest grades of soap.

These studies revealed that the capsules (heads) of oil-bearing poppy contain on an average from 0.5 to 0.8% of morphine, although tonnes of these capsules after removal of the seeds for oil production were discarded as production wastes.

Hence, a very cheap and economically profitable source of morphine was found, and to date the production of morphine from the opium produced from oil-bearing poppy capsules has been organized in the USSR and other countries.

Morphine Hydrochloride (*Morphini hydrochloridum*)



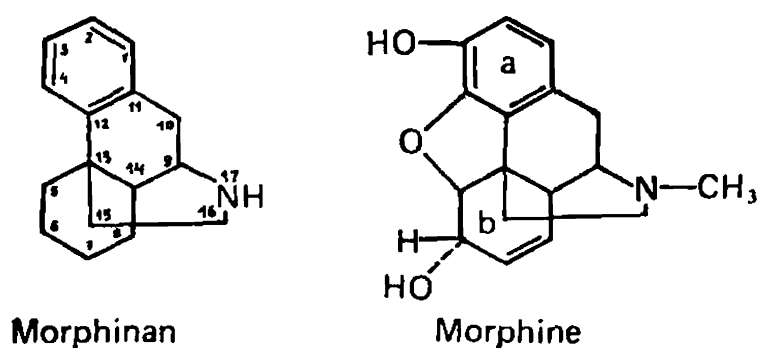
$C_{17}H_{19}NO_3 \cdot HCl \cdot 3H_2O$

M.m. 375.85

Morphine as a drug that strongly alleviates pain has been serving medicine more than one-and-a-half centuries. Morphine was the first alkaloid to be discovered. It was exactly what inaugurated the era of the further discovery of the alkaloids as a large independent class of natural organic compounds.

Morphine was first isolated from opium in 1804 by the French pharmacist A. Seguin, and later in 1806 F. Serturner isolated it in the pure crystalline form and described it as a base. This circumstance altered the previously existing view that plants contain only an acidic or neutral substances. In over 100 years after the discovery of morphine, its structural formula was established, which was then confirmed by synthesis having only a theoretical significance. Many eminent chemists (L. Knorr, A. Freund, H. Vongerichten, later R. Robinson and others) worked on the establishment of morphine's structure.

The basis of the complicated structure of morphine is morphinan. Morphine is its epoxy derivative:



The presence of characteristic functional groups in a morphine molecule (the phenol hydroxyl group in ring a and the secondary alcohol group in ring b) underlies the formation of numerous derivatives used as medicaments. The most important of them are the esters of morphine formed via the phenol hydroxyl group (the drugs codeine and ethylmorphine hydrochloride). Another morphine derivative employed in medicine is apomorphine. It is produced by heating morphine, which loses two water molecules.

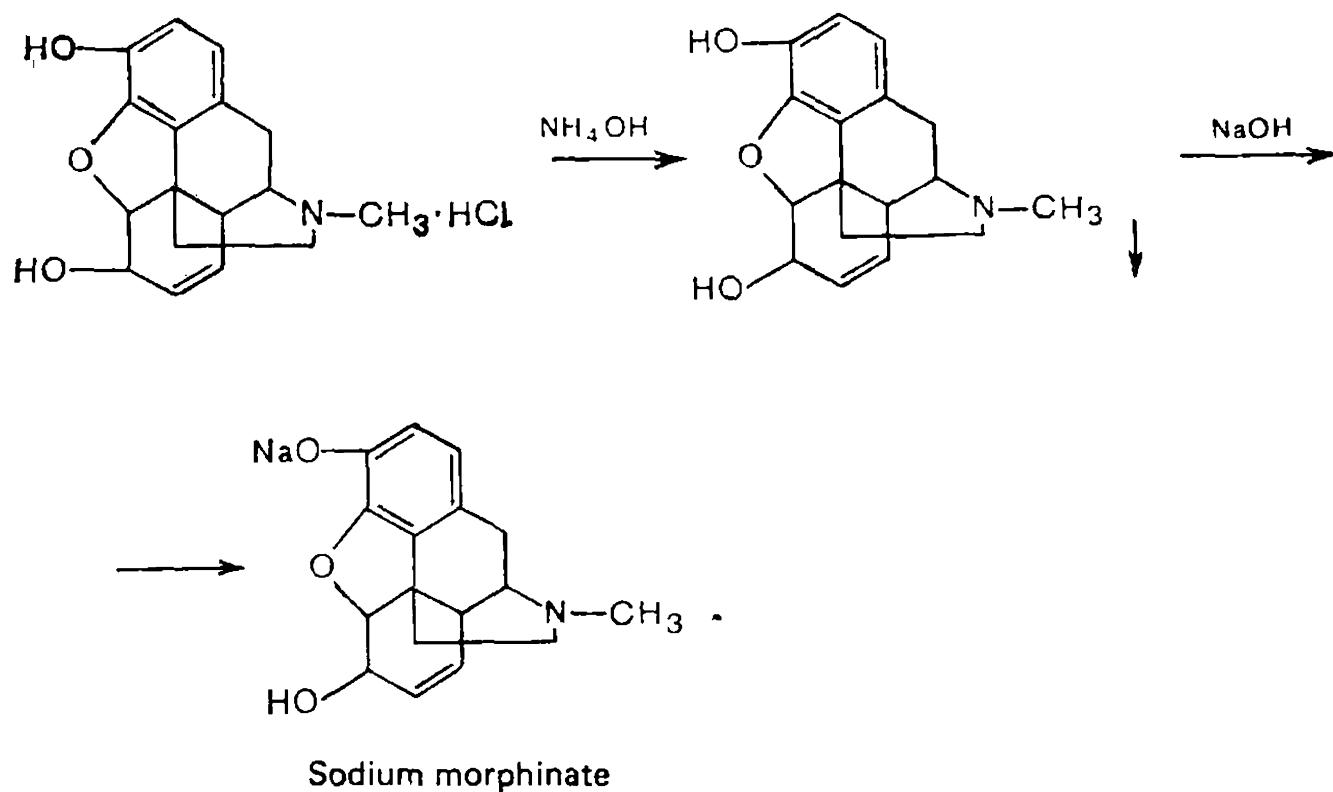
Having an N-methyl group in its molecule (tertiary nitrogen), morphine is a quite strong tertiary base capable of yielding salts with acids.

Morphine hydrochloride is employed in medicine. It forms white acicular crystals or a white crystalline powder that becomes slightly yellow in storage. Morphine hydrochloride dissolves slowly in water, sparingly in alcohol, and is practically insoluble in chloroform and ether.

The identification reactions of the drug are based on its chemical properties and functional groups. The presence of a phenol hydroxyl group in the molecule is confirmed by:

(a) a reaction with Marchi's reagent (formaldehyde + sulphuric acid); a purple colour appears that rapidly transforms to blue-violet (a distinction from codeine);

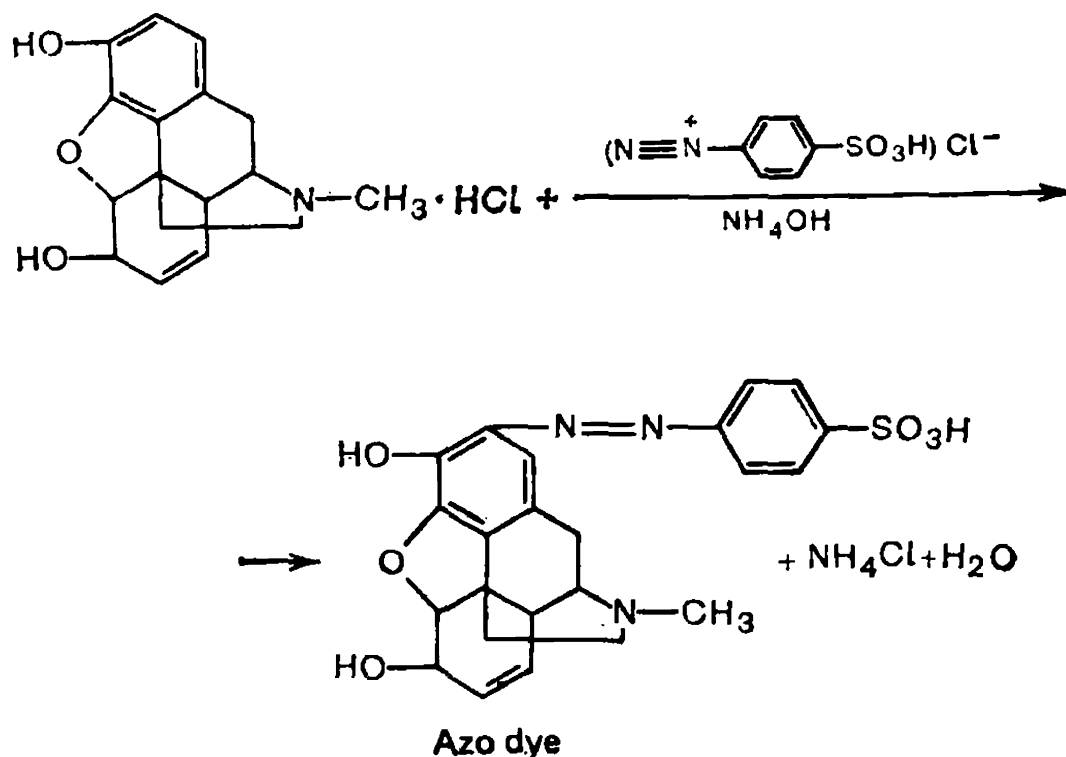
(b) precipitating the morphine base with an ammonia solution and then dissolving it in an excess of an alkali (NaOH):



The above official reactions for the phenol hydroxyl group can be augmented by others, namely:

a reaction with an iron(III) chloride solution; a blue-violet colour appears;

a coupling reaction with diazonium salts in an alkaline medium (the formation of an azo dye):



Morphine forms precipitates of various colours with the group alkaloid reagents. The most sensitive reaction is that with a solution

of ammonium molybdate in the presence of concentrated sulphuric acid (a violet colour turning blue, when allowed to stand the colour turns green). This reaction is indicated by the State Pharmacopoeia as an identification one.

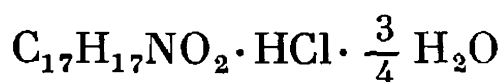
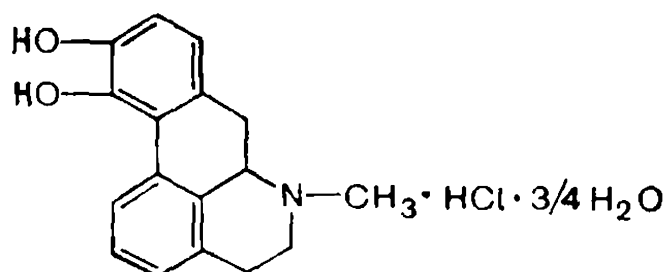
The content of the drug is determined by acid-base titration in non-aqueous media (State Pharmacopoeia).

Morphine is administered as a strong pain-alleviating agent during the postoperative period to patients suffering from malignant tumours and other severe diseases attended by great pain. Morphine causes a pleasant feeling and drowsiness (a euphoric state). The repeated taking of morphine causes drug addiction. This is a major shortcoming of the drug.

It is taken orally and more often subcutaneously. It is dispensed in powders and ampoules containing 1 or 10 ml of 1% and 5% solutions.

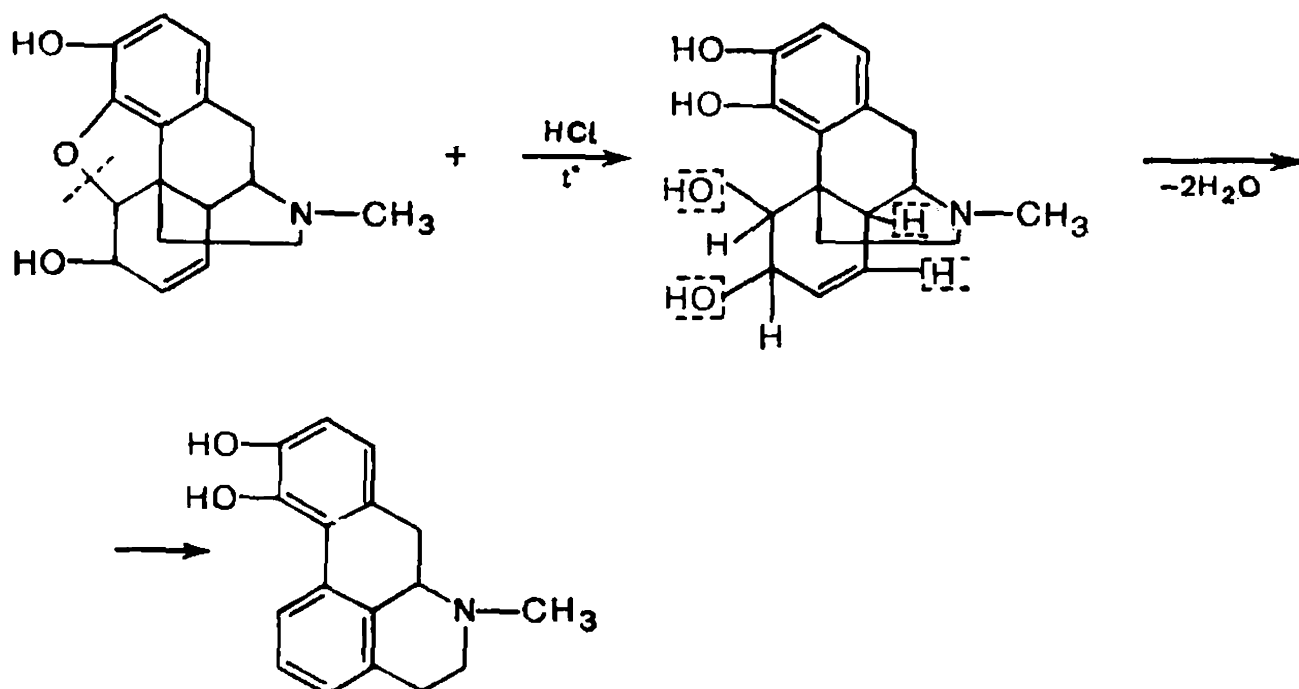
It should be stored in a locked cupboard in well closed orange-glass jars in a place protected from light. It is listed in Group A.

Apomorphine Hydrochloride (*Apomorphini hydrochloridum*)



M.m. 317.30

The drug is produced from morphine by heating it with hydrochloric acid:



Apomorphine hydrochloride is a white slightly grayish or slightly yellowish crystalline powder. It dissolves with difficulty in water and alcohol, and is insoluble in ether and chloroform.

Apomorphine contains two phenol hydroxyl groups and exhibits a much greater tendency of oxidation than morphine. Its reducing properties are therefore more pronounced. As a result of oxidation in air and in light, the drug turns green, and its activity disappears.

When oxidizing agents react with apomorphine, oxidation products form that have various colours, which is used to identify the drug.

When the latter is reacted with an iodine solution in the presence of sodium hydrogen carbonate and the reaction mixture is agitated with ether, the ether layer turns red-violet, while the water layer turns green. When the drug is reacted with a nitric acid solution, the oxidation products turn blood-red.

The specific rotation of apomorphine (from -46° to -53°) can be used to identify the drug and check its purity.

The content of apomorphine in the drug is determined by acid-base titration in non-aqueous media.

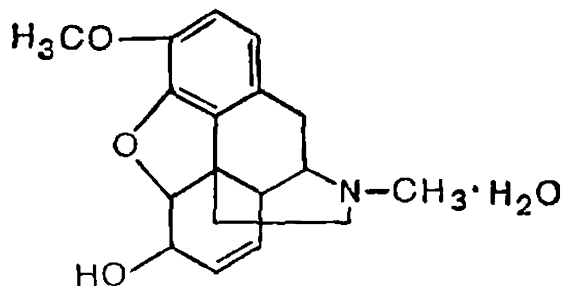
Apomorphine is administered as an emetic and expectorant in poisoning. It is prescribed orally and subcutaneously, and is dispensed in powders. Since it is readily oxidized, its solutions are prepared *ex tempore*.

It should be stored in a locked cupboard in well closed orange glass jars. It is listed in Group A.

Morphine ethers. Of the morphine ethers formed via the phenol hydroxyl group, widespread application in medicine has been found by the methyl ether (codeine) and ethyl ether (ethylmorphine hydrochloride—dionine). The former (codeine) is one of the alkaloids of opium, while the latter is a synthetic drug.

The pharmacopoeial drugs of the morphine ethers are codeine, codeine phosphate, and ethylmorphine hydrochloride.

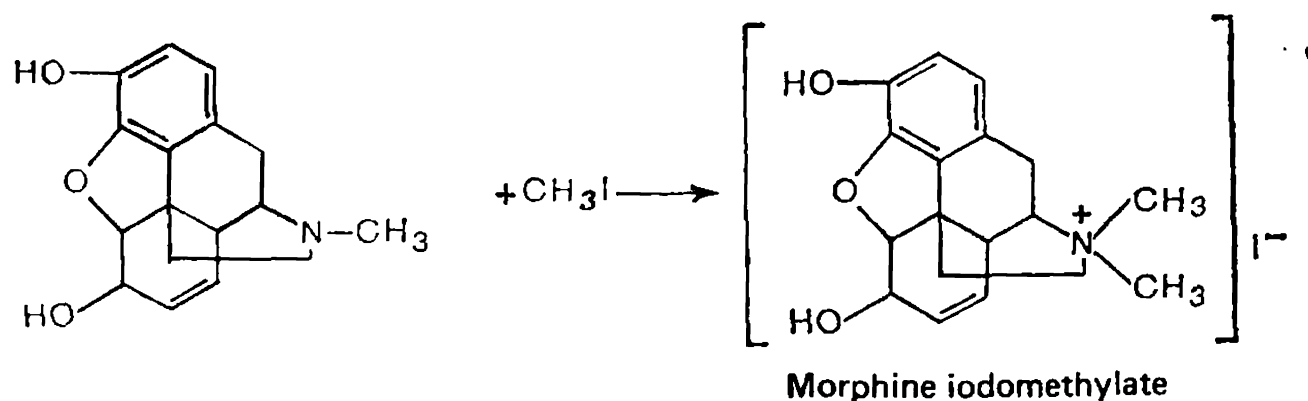
Codeine (*Codeinum*)



M.m. 317.39

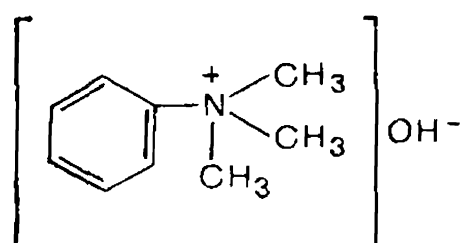
Codeine is produced for medical purposes from morphine by its methylation, using a semisynthetic process. There are various variants of methylating morphine differing in the methylating

agent. But not all methylating agents can be used for this purpose. For example, methyl iodide CH_3I cannot be used to produce codeine because it enters into a reaction with the tertiary nitrogen to form morphine iodomethylate:

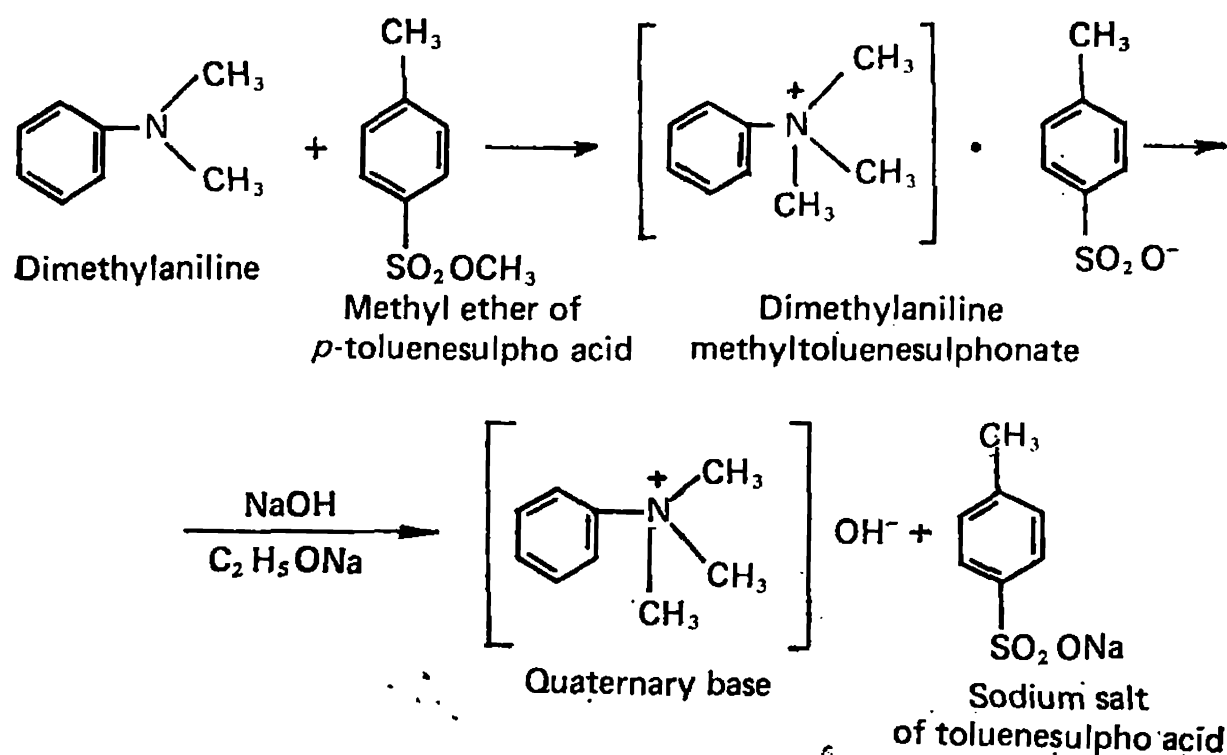


This is why only such methylating agents can be used that do not react with the tertiary nitrogen, for example, quaternary bases.

Trimethylphenylammonium hydroxide (a quaternary base) was found to be the best methylating agent. Its formula is:

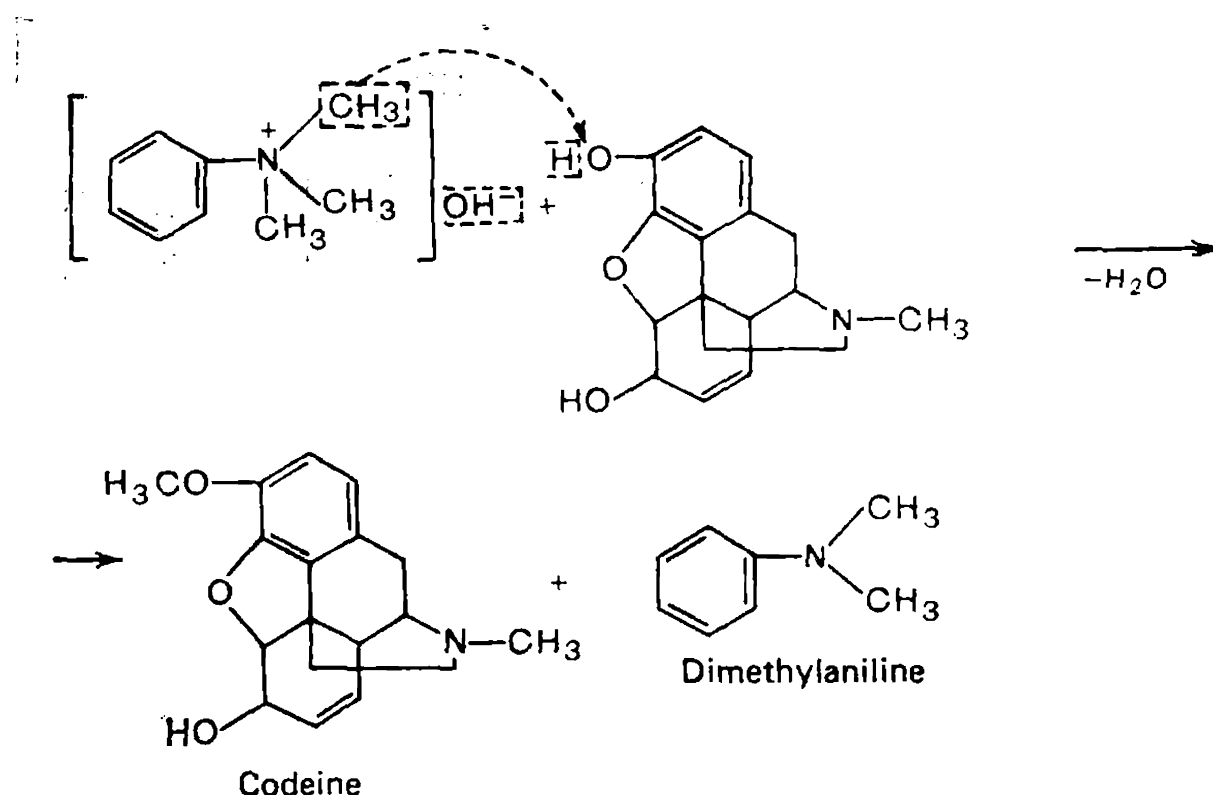


This quaternary base is produced from dimethylaniline by the method proposed by V. Rodionov and D. Shaposhnikov:



In this method, the previously employed costly methylating agent CH_3I is replaced by a cheaper one—the methyl ether of *para*-toluene-sulpho acid (a production residue).

The methylating of morphine occurs as follows:



The formed dimethylaniline is recycled to the production process. This method of the semisynthetic production of codeine is a commercial one.

Codeine forms colourless crystals or a white crystalline powder with a bitter taste. It weathers in the air. It dissolves poorly in water, but does dissolve in hot water. It dissolves readily in alcohol, chloroform, and dilute acids.

Being a methyl ether of morphine, codeine does not dissolve in alkalies, and reacts with iron(III) chloride only after saponification of the methoxy group. The reaction with Marchi's reagent (a blue colour) proceeds better with heating and after a certain time elapses (the sulphuric acid first saponifies the methoxy group). Unlike morphine, the codeine base reacts with concentrated nitric acid to form an orange colour.

Since codeine is produced from morphine, the latter may be contained as an admixture, and the State Pharmacopoeia recommends determining its content.

The content of the drug is determined by neutralization. Since the drug dissolves poorly in water, the sample is first dissolved with slight heating in a small amount of alcohol, next freshly boiled cooled water is added, and titration is conducted with hydrochloric acid using a methyl red indicator.

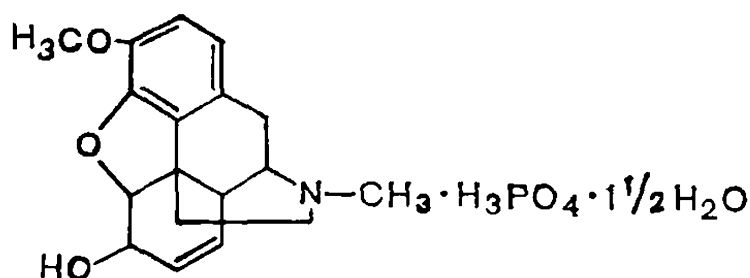
The analgesic (narcotic) action of codeine is considerably weaker than that of morphine, but it has gained an especial value in allaying irritating cough.

Codeine does not cause drug addiction in small doses and is much less toxic. Codeine and its salts are listed in Group B. Nevertheless, codeine in large doses and with prolonged administration may cause addiction, therefore it is never released without a doctor's prescription.

The drug is dispensed in 0.015-g powders and tablets.

It should be stored in well closed containers protecting it from the action of light.

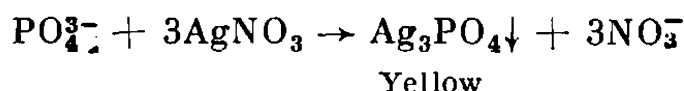
Codeine Phosphate (*Codeini phosphas*)



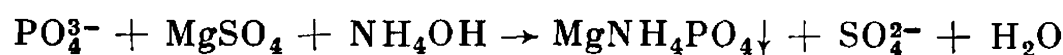
M.m. 424.4

Codeine phosphate is a white crystalline powder with a bitter taste. It weathers in the air. It dissolves readily in water, sparingly in alcohol, ether, and chloroform.

The methoxy group in the codeine phosphate molecule underlies the reactions characteristic of codeine. Additionally, reactions are conducted for the phosphate ion (with a magnesia mixture or a silver nitrate solution):



Yellow



White

When codeine phosphate is reacted with an alkali solution, the codeine base precipitates. It is filtered, dried, and its melting point is determined, which should be 154-157 °C.

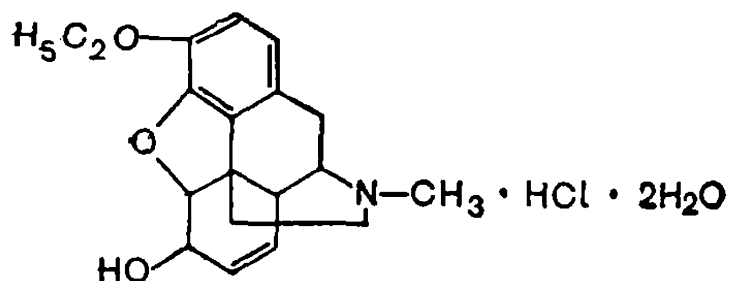
All these reactions are used for identifying the drug.

The State Pharmacopoeia recommends determining the content of the drug by acid-base titration in non-aqueous media.

Codeine phosphate has the same applications as the codeine base. It is dispensed in 0.015-g powders and tablets.

The conditions of storage are the same as for codeine.

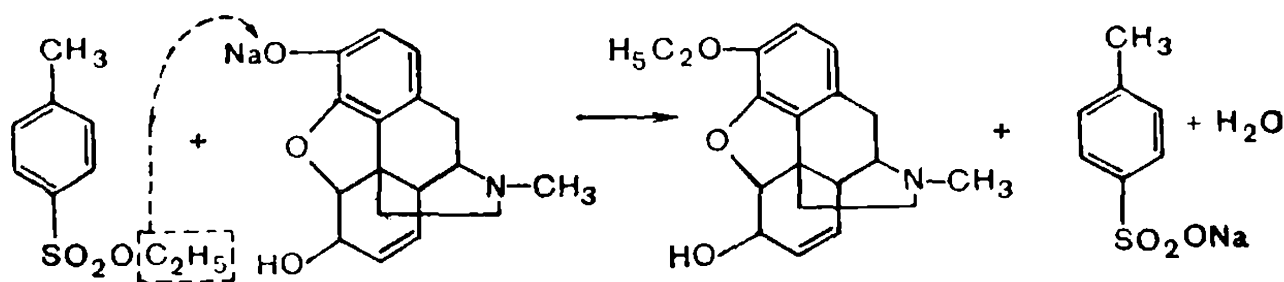
Ethylmorphine Hydrochloride (*Aethylmorphini hydrochloridum*)



$C_{19}H_{23}NO_3 \cdot HCl \cdot 2H_2O$

M.m. 385.89

Ethylmorphine hydrochloride is produced in the same way as codeine, by the ethylation of morphine. In this case, ethyl iodide C_2H_5I could be used as the ethylating agent because it does not enter into a reaction with the tertiary nitrogen and does not form iodoethylates. But ethyl iodide, like methyl iodide, is a costly reagent, therefore to cut production costs, it was proposed to use the ethyl ether of *para*-toluenesulpho acid as the ethylating agent. Morphine enters into a reaction with this reagent in the form of its sodium salt—sodium morphinate:



Ethylmorphine hydrochloride is a white crystalline powder with a bitter taste. It dissolves in water and alcohol, sparingly in chloroform, and very poorly in ether.

Its identity is determined by a reaction for the phenol hydroxyl group with an iron(III) chloride solution after heating the drug with sulphuric acid. Unlike codeine, first a green colour appears, and after the addition of a drop of dilute nitric acid, it turns red (State Pharmacopoeia).

All the other reactions for codeine can also be used for the given drug.

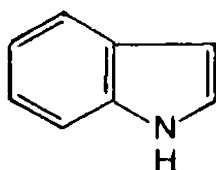
The content of the drug is determined by acid-base titration in non-aqueous media.

As regards its physiological action, ethylmorphine hydrochloride occupies an intermediate position between morphine and codeine. Ethylmorphine hydrochloride is chiefly employed in ophthalmology in the form of drops and an ointment as an anti-inflammation agent and for the same indications as codeine.

It is dispensed in 0.01- and 0.015-g powder and tablets.

It should be stored in a locked cupboard in well closed orange glass jars. It is listed in Group A.

28.4. INDOLE DERIVATIVES

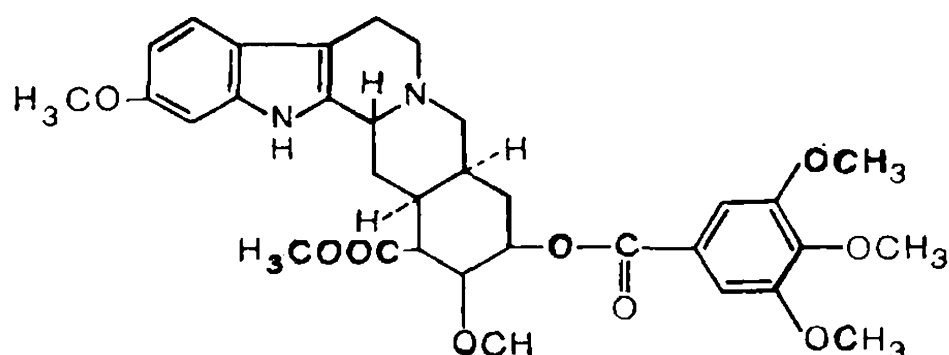


The molecules of the alkaloids of this group contain the indole ring. Indole alkaloids are quite abundant in the plant world, but only a few of them have found application in medicine, namely, eserine (physostigmine), strychnine and its analogue securinine, reserpine, and the alkaloids of ergot—ergometrine and ergotamine.

The structure of all these alkaloids is very complicated and diverse, and they are united into a single group only by the presence in their molecules of an indole ring. Their natural sources also vary.

As regards its chemical properties, each of these alkaloids is individual, and therefore has its specific methods of analysis.

Reserpine (*Reserpinum*)



$C_{33}H_{40}N_2O_9$

M.m. 608.70

Reserpine was first discovered in the leaves and roots of *Rauwolfia serpentina* (the *Apocynaceae* family) growing in tropical and subtropical climatic zones, chiefly in India, where the healing effect of this plant was first discovered. It has also been obtained from the Australian species *constricta*.

The Hindus were the first to use extracts from the roots and leaves of *Rauwolfia serpentina* to treat various nervous and psychic diseases, epilepsy, etc. When Indian doctors established the tranquilizing and hypotensive action of this drug and published the results of their observations, *Rauwolfia serpentina* attracted the attention of pharmacologists and chemists in many countries.

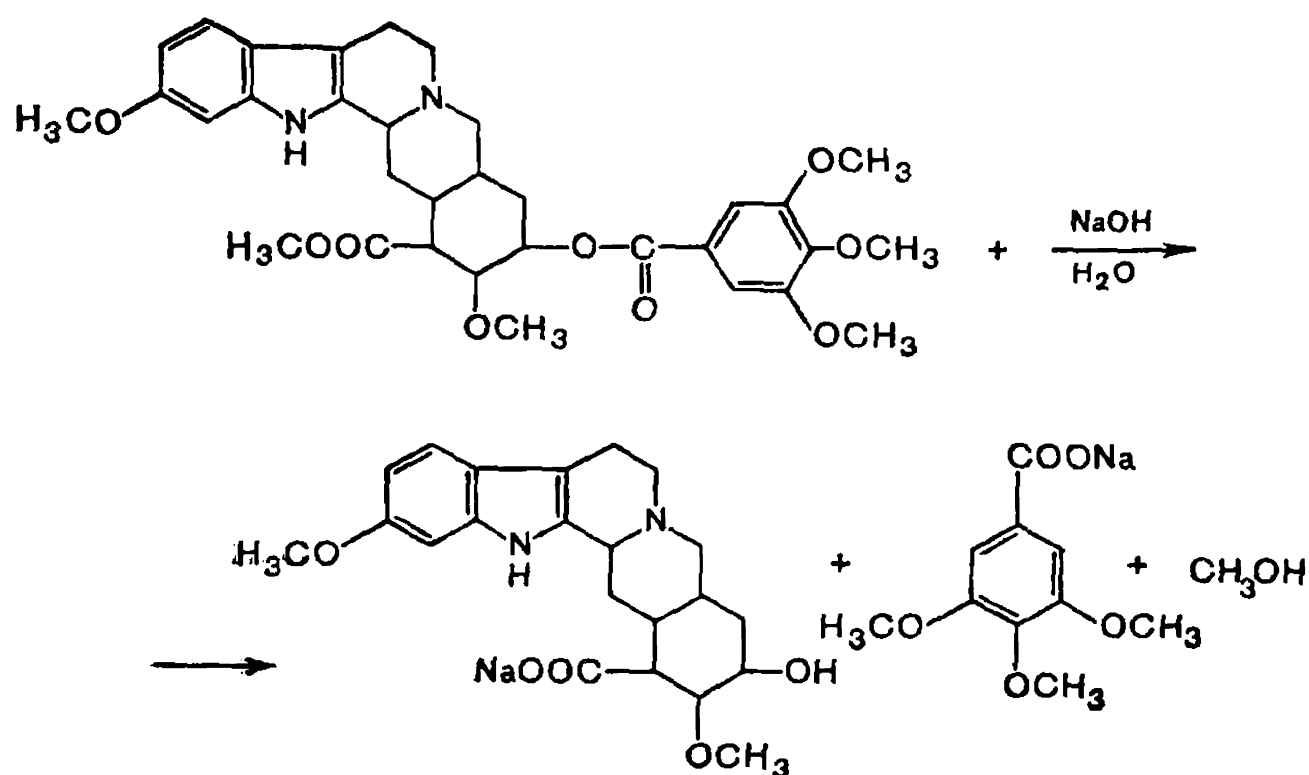
The genus *rauwolfia* was named in honour of the German doctor, botanist, and traveller Leonhard Rauwolf, well known in his time (16th century), who was the first to give a botanical description of this plant.

Reserpine is not the only alkaloid of *Rauwolfia serpentina*. This plant, especially its roots, contains over 40 alkaloids, of which the alkaloids reserpine, serpentine, and yohimbine are of the greatest interest. Reserpine is the most pharmacologically active alkaloid. It is a pharmacopoeial drug and is widely employed in medicine as a hypotensor.

For a long time reserpine was produced from natural sources by extracting all the alkaloids with their subsequent chromatographic separation. But after its synthesis, the production of reserpine from natural sources gave way to its synthetic commercial production, which considerably cut the cost of this very valuable and widely employed drug.

Reserpine was first synthesized completely in 1956 by R. Woodward (USA), and somewhat later the synthetic production of reserpine was developed in the USSR by professor O. Magidson and his collaborators.

The alkaline hydrolysis of reserpine (for example, with NaOH) yields the relevant (sodium) salts of reserpinic and trimethoxybenzoic acids and methanol:

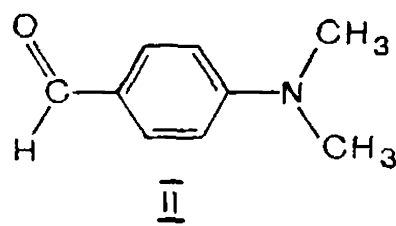
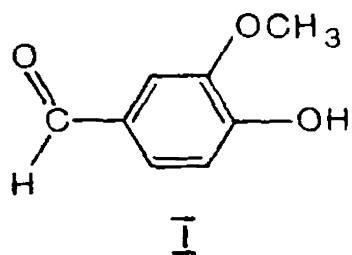


The products of the alkaline hydrolysis of reserpine confirm that it is a double ester of reserpinic acid, which as an alcohol acid is esterified relative to the carboxyl group by methanol and relative to the secondary alcohol group by trimethoxybenzoic acid.

Reserpine is a white or yellowish finely crystalline powder sparingly soluble in water, alcohol, and ether, and readily soluble in chloroform and acetic acid. Reserpine solutions, especially acidified ones, rapidly turn yellow in the light, becoming partly decomposed.

To identify the drug, oxidation of reserpine is used, which is due to the presence of an indole ring and methoxy groups in the aromatic rings of its molecule. The oxidation products depending on the nature of the oxidizing agent have various colours. For example, a green colour and fluorescence of the solution appear with a sodium nitrite solution in the presence of sulphuric acid (State Pharmacopoeia); a purple colour appears with chlorine water, a yellow-lilac one with hydrogen peroxide, a red colour turning light blue with Froehde's reagent (molybdic acid + sulphuric acid), and a dark lilac colour with a potassium permanganate solution.

The indole ring is also characterized by colour condensation reactions with aldehydes, for example, a pink colour appears with vaniline (I) in the presence of hydrochloric acid (State Pharmacopoeia), and a green colour that turns red appears with dimethylaminobenzaldehyde (II) in the presence of glacial acetic and sulphuric acids:



The State Pharmacopoeia also recommends using spectral data for a qualitative characteristic of reserpine. Thus, according to the State Pharmacopoeia, a 0.002% solution of the drug in 95% alcohol should have a maximum absorption at a wavelength of 268 nm. The optical density of this solution in a cell with a layer thickness of 1 cm at a wavelength of 268 nm should be about 0.55.

Since reserpine is a weak base, its content in a drug is determined by acid-base titration in non-aqueous media (State Pharmacopoeia).

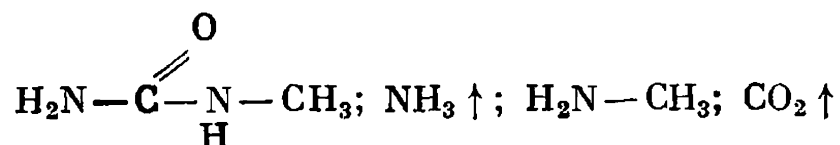
Reserpine is administered in hypertension to lower the arterial blood pressure.

It is dispensed in 0.0001- and 0.00025-g powders and tablets.

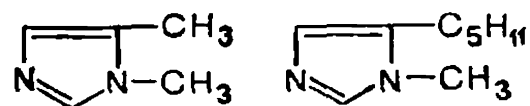
Crystalline reserpine is stored in a locked cupboard (Group A), while tablets are stored with care (Group B) in closed jars in a dry place protected from light.

A drug named raunatine that contains several alkaloids of *Rauwolfia serpentina* has been produced in the USSR. The drug exhibits a hypotensive and anti-arrhythmic action and is dispensed in 0.002-g tablets. It is listed in Group B.

oxidation products:



On the other hand, when pilocarpine was heated with soda lime, bases of the imidazole series were obtained:

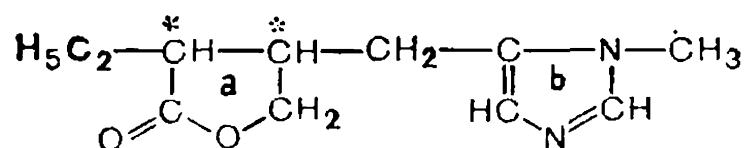


1,5-Dimethylimidazole

1-Methyl-5-amylimidazole

These products of decomposition of natural pilocarpine indicate that the pilocarpine molecule consists of pilopic or homopilopic acid and methylimidazole. The final structure of pilocarpine was confirmed by its synthesis, which was first carried out by Soviet chemists—professor N. Preobrazhensky and his collaborators (1933).

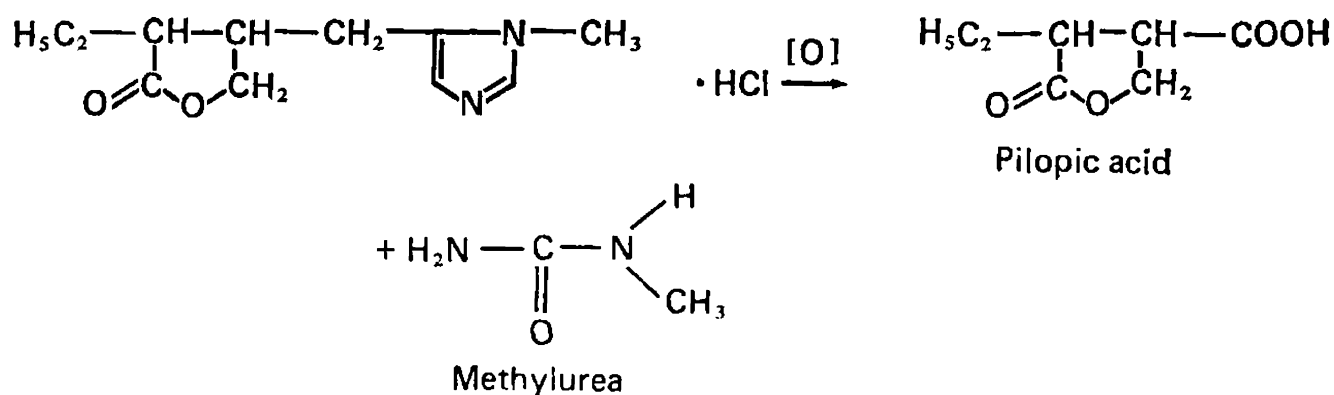
From the chemical viewpoint, pilocarpine is a ditertiary base with an N-methyl group. It is optically active. The optical isomerism is due to two asymmetric carbon atoms in the lactone ring (a) of the molecule:



Pilocarpine is the dextrorotatory (d) isomer.

Pilocarpine hydrochloride forms colourless crystals or a white crystalline powder without an odour. It is hygroscopic, dissolves readily in water, alcohol, and is virtually insoluble in ether and chloroform.

Pilocarpine is identified by oxidation reactions because the oxidation products are customarily coloured. These products are most frequently homopilopic or pilopic acid (with strong oxidation) and monomethylurea (a decomposition product of the imidazole ring):



The methylurea can be further oxidized to carbon dioxide, ammonia, and methylamine $\text{H}_2\text{N}-\text{CH}_3$. The oxidation products can vary depending on the nature of the oxidizing agent.

The official identification reaction of pilocarpine is its oxidation with hydrogen peroxide and potassium dichromate in the presence of sulphuric acid. After the addition of chloroform, the reaction mixture is vigorously agitated, then allowed to settle, and the chloroform layer acquires a blue-violet colour.

When a 5% solution of sodium nitroprusside in an alkali medium is added to an aqueous solution of the drug, the solution turns cherry red (Legal's test for the five-membered lactone ring).

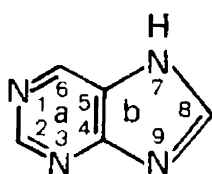
Since pilocarpine is optically active, the State Pharmacopoeia recommends determining the specific rotation, which should range from $+88.5$ to $+91^\circ$ (a 2% aqueous solution).

The content of the drug is determined by acid-base titration in non-aqueous media (State Pharmacopoeia).

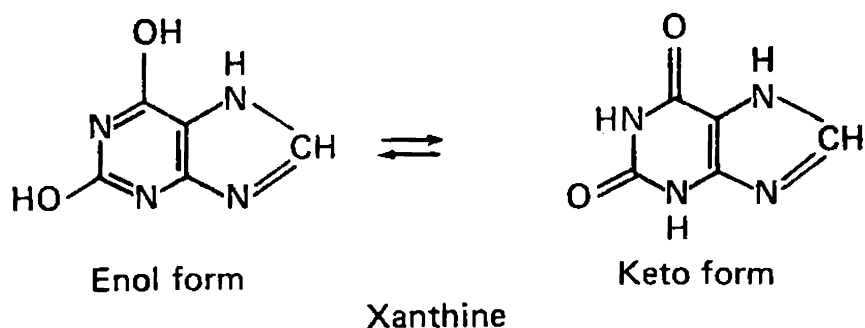
Pilocarpine is widely used in ophthalmology to treat glaucoma. It is prescribed in the form of 1 and 2% solutions as eye drops, and also in the form of a 1% and 5% ointment for the same purpose and in the form of eye films; the drug is also prescribed for subcutaneous administration. To prolong the action of pilocarpine, a definite amount of methylcellulose, sodium carboxymethylcellulose, or polyvinyl alcohol is added to its solutions.

It is dispensed in the form of a powder, 1% and 2% solutions, and a 1% and 5% ointment. It should be stored in a locked cupboard in well closed containers protecting it from the action of light and moisture. Pilocarpine films are stored at a temperature of 15 to 25°C . The drug is listed in Group A.

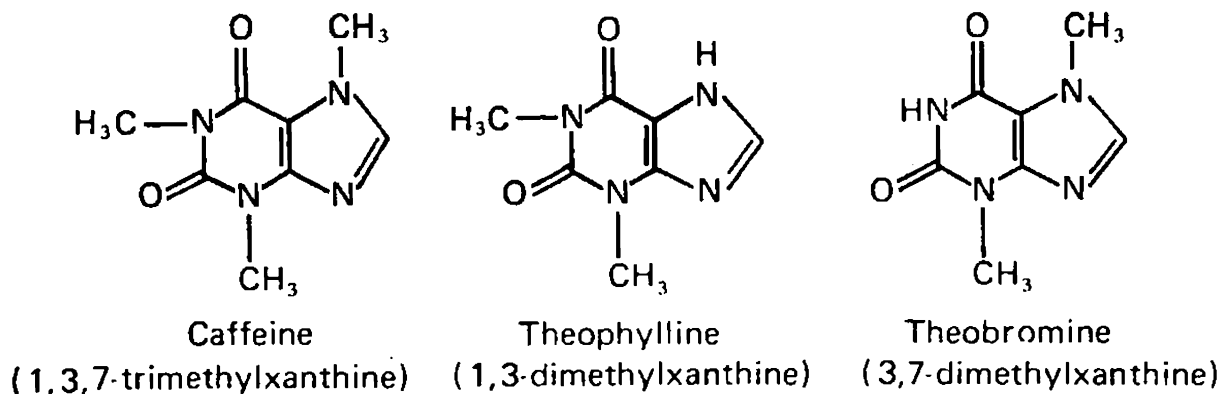
28.6. PURINE DERIVATIVES



Purine is a bicyclic system consisting of a pyrimidine (a) and imidazole (b) rings. The hydroxylated derivative of purine is called **xanthine**, which can exist in both the enol and keto forms:



Of importance for medicine is not xanthine, but its methylated derivatives caffeine, theobromine, theophylline, and their derivatives:

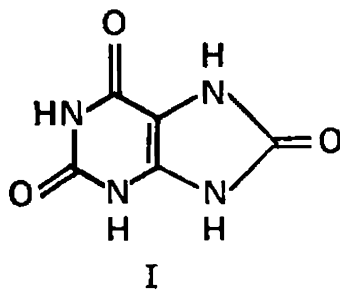


The use of alkaloids of the purine series in medicine is based on their stimulating action on the central nervous system. This action is exhibited especially strongly by caffeine (a tonic). Theobromine and theophylline have a diuretic action, and in addition they dilate the coronary vessels.

The natural sources of the alkaloids of the purine series are the leaves of the tea plants (caffeine, theophylline), the seeds of the coffee plant (caffeine, theophylline), the husks of cocoa beans (theobromine), whence these alkaloids were extracted with organic solvents.

In addition to alkaloids, the leaves of the tea plant contain many accompanying substances (tanning substances, proteins, carbohydrates, resins, nucleoproteides, enzymes, etc.), therefore the extracts have to be thoroughly purified from these admixtures.

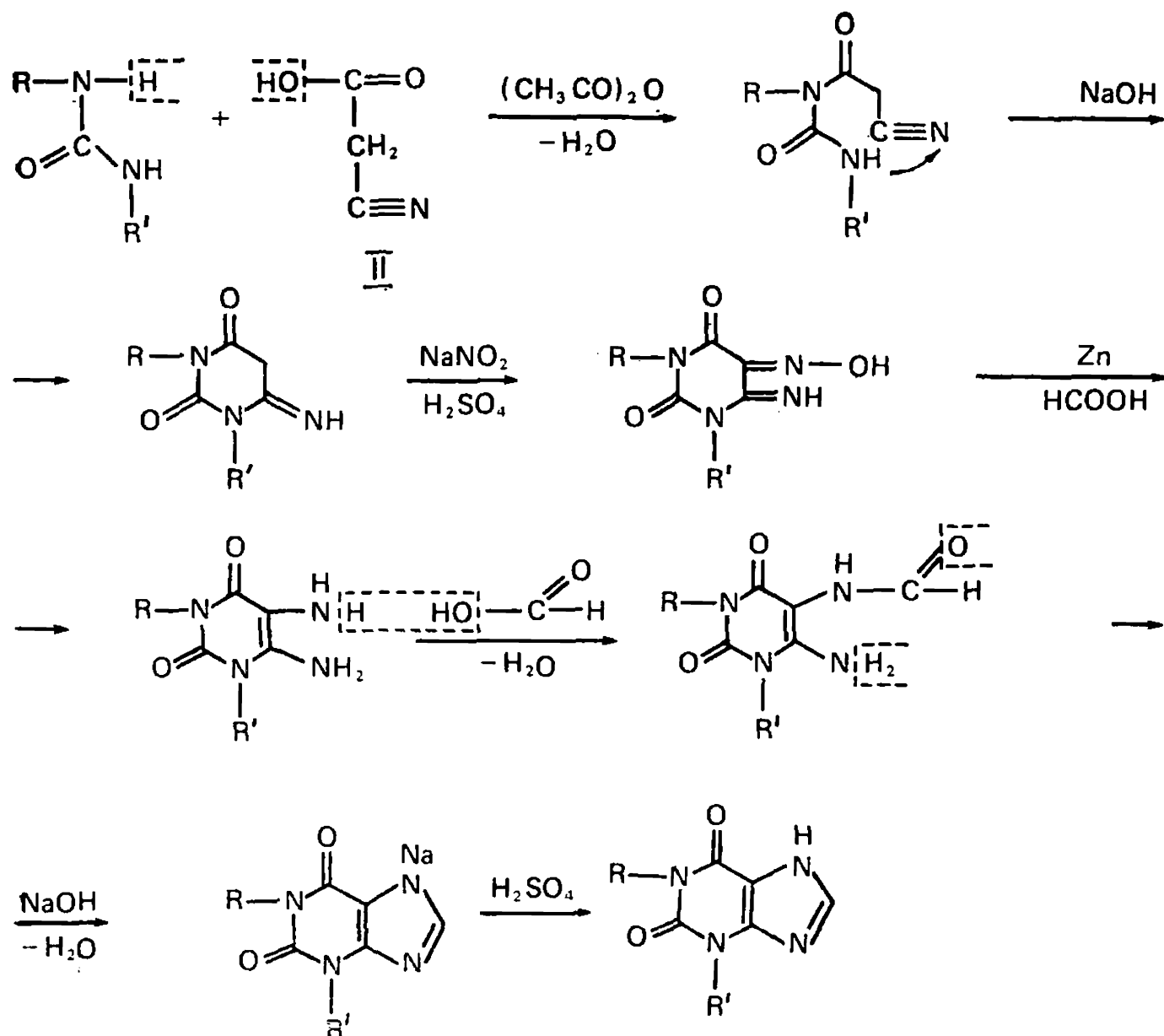
At present, purine alkaloid drugs are produced synthetically from substances that contain a purine ring, for example uric acid (I), or from substances that are not purines, but that acquire the structure of a purine ring by a number of transformations.



In the first case, the method is a semisynthetic one, and in the second complete synthesis occurs. A semisynthetic method of producing purine alkaloids from uric acid was developed in the USSR by O. Magidson *et al* and became quite popular.

Traube's synthesis, which in a modified form is used at present in commercial production, is a classical method of the complete synthesis of purine alkaloids. By this method any xanthine deriv-

ative can be produced from various alkyl derivatives of urea. The starting substances for Traube's synthesis are alkyl (mono- or di-) derivatives of urea and cyanoacetic acid (II):

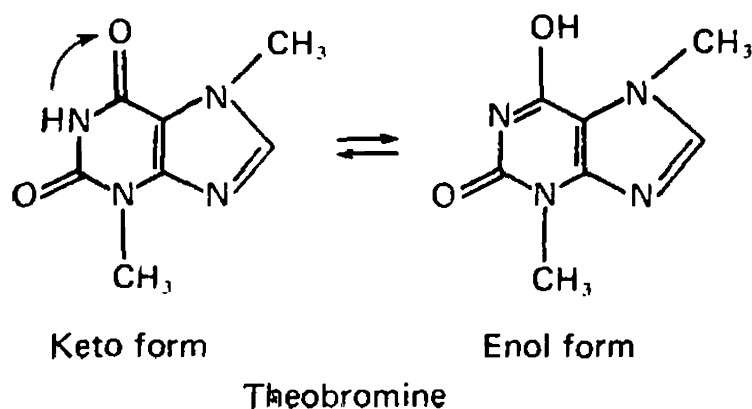


where R and R' are CH₃ or H. When R and R' are CH₃, the product is theophylline.

During the last years, methods of producing purine alkaloids by the direct methylation of xanthine have been developed. It has been established that the yield of caffeine in the methylation of xanthine with dimethyl sulphate depends to a considerable extent on the pH of the medium. In an alkaline medium (pH = 8-9), the xanthine is completely methylated, i.e. caffeine forms. At a pH of 4-7, substitution occurs in positions 3 and 7, which results in the formation of theobromine.

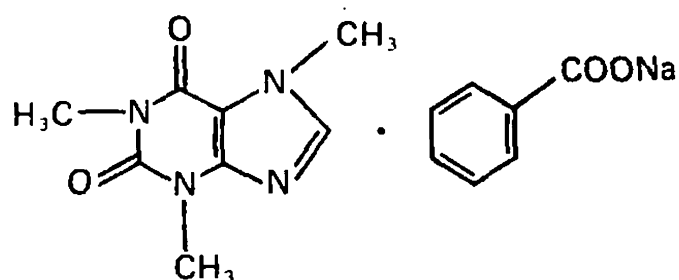
Caffeine, theobromine, and theophylline are very weak bases. Their basic properties are due to the nitrogen in position 9 of the imidazole ring. Their salts with mineral acids do not virtually exist because they readily hydrolyze.

Theobromine and theophylline are amphoteric substances. The acidic properties of theophylline are due to the hydrogen of the imide group in position 7, and of theobromine to the hydrogen of the imide group in position 1. The hydrogen can migrate to the neighboring oxygen with the formation of the enol form:

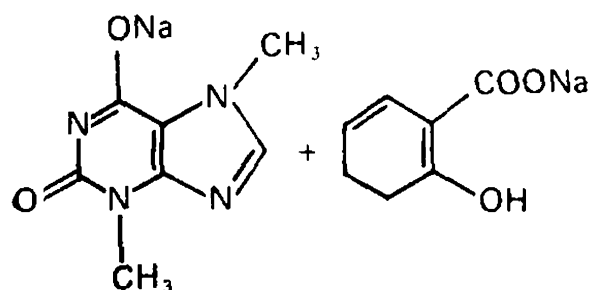


The hydrogens of the imide groups in caffeine are substituted by methyl radicals, therefore it has no acidic properties, while the basic properties are so weak that it can be considered as a practically neutral substance.

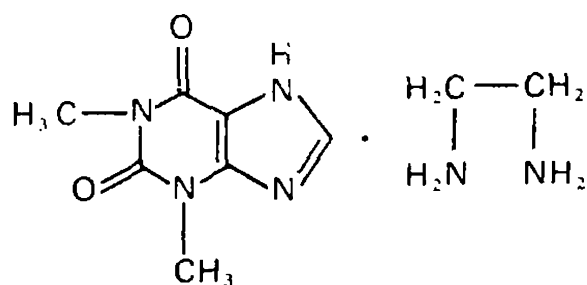
All the alkaloids of the purine series dissolve poorly in water. Caffeine and theophylline dissolve readily only in hot water. The solubility of caffeine increases substantially in organic acids (benzoic, salicylic) and their salts; it has been established here that the formed complexes contain equal parts of caffeine and an acid. An example of such a complex is caffeine and sodium benzoate, which is a pharmacopoeial preparation:



Theophylline and theobromine, owing to their acidic properties, form water-soluble salts with metals (theobromine-sodium, themisal) and organic bases (euphylline):



Themisal



Euphylline

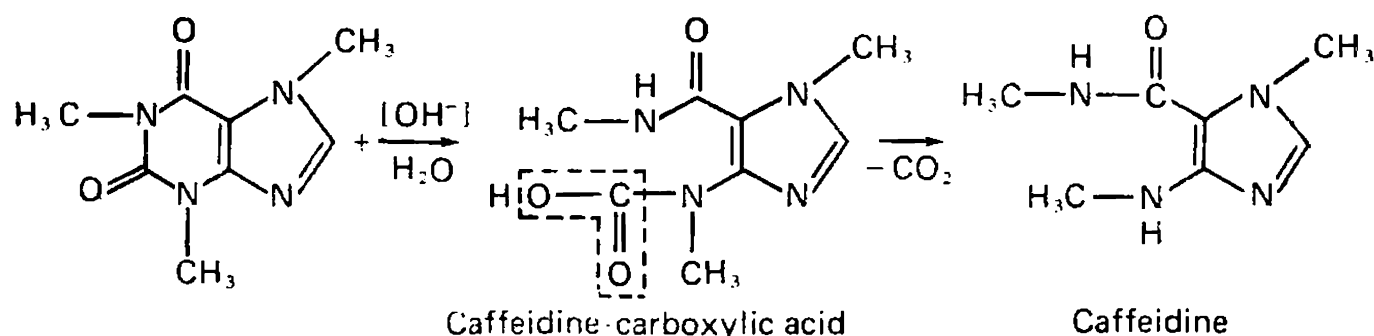
The ability of theophylline and theobromine to form salts with metals is employed for their identification. For example, theophylline and theobromine are identified by reactions yielding their silver and cobalt salts.

The silver salt of theophylline forms in the cold, and white crystals precipitate.

A gelatin-like silver salt of theobromine forms when heated. Thus, the appearance of these salts enables one to distinguish theobromine from theophylline.

The cobalt salts of theobromine and theophylline are coloured differently, which also makes it possible to distinguish one drug from the other.

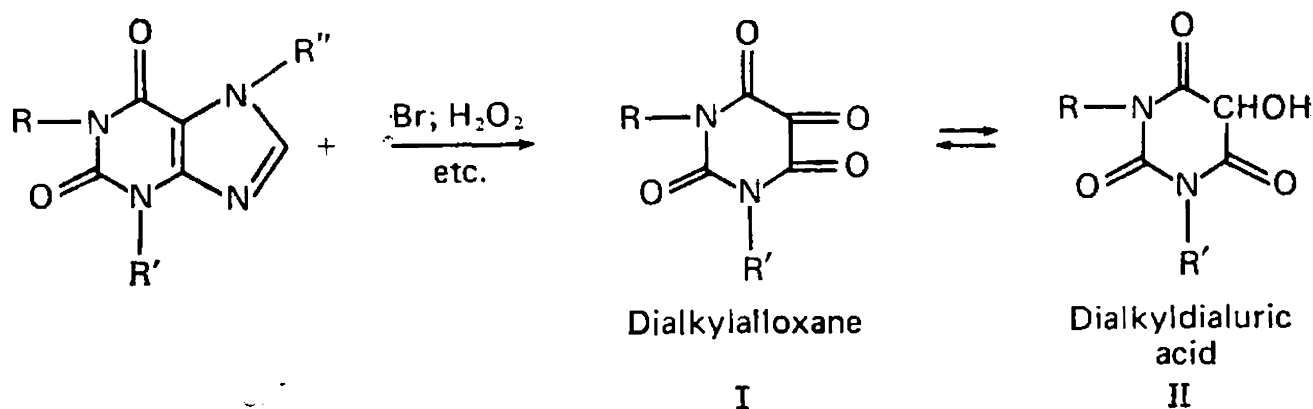
The purine alkaloids are unstable when heated in an alkaline medium (at $\text{pH} > 9$). In this case, caffeine decomposes to caffeidine-carboxylic acid and further to caffeidine (a physiologically inactive substance):



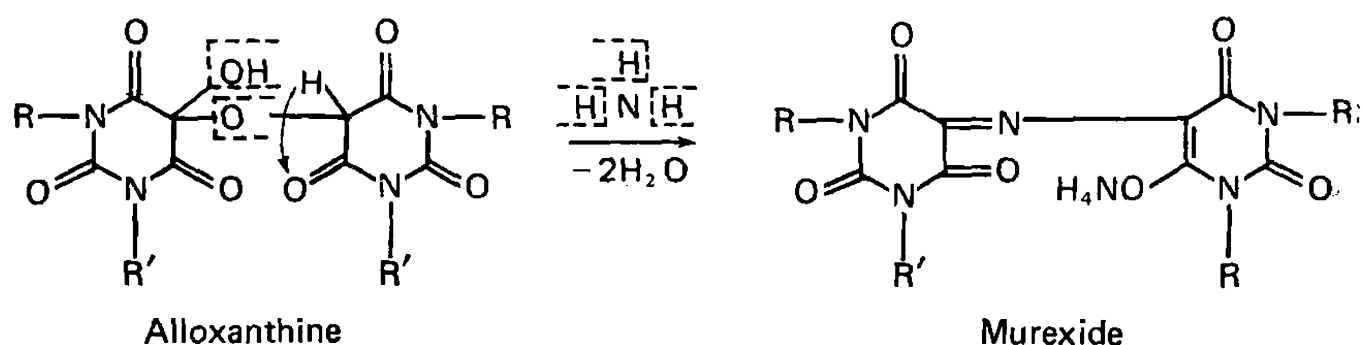
Theophylline has a similar reaction. Theobromine is the most stable to the action of alkalis and under the same conditions with theophylline decomposes only partly.

Hence, theophylline forms a salt with an alkaline solution in the cold, but when heated with such a solution it decomposes and loses its physiological activity.

The murexide test (a reaction of murexide formation) is a group reaction for the alkaloids of the purine series. It consists in heating a substance containing the purine ring with an oxidizing agent (bromine water, perhydrol, nitric acid, etc.) and then treating it with an ammonia solution; a crimson colour appears because of the formation of the ammonium salt of purpuric acid:



These two tautomeric forms (I) and (II) react with each other and form alloxanthine:



If potassium hydroxide is used instead of ammonia, the potassium salt of purpuric acid will be coloured blue-violet.

The murexide test was considered for a long time to be a reaction specific for purine derivatives, but it later became known that the murexide test also characterizes certain other compounds not containing the purine ring in their molecule, such as alloxan, dialuric, barbituric, and violuric acids, i.e. compounds containing a pyrimidine ring in their molecule. To date, however, the murexide test is a group reaction for detecting purine alkaloids and is an official one.

A variety of methods are used for the quantitative determination of the purine alkaloids that depend on their chemical properties. Since all these alkaloids are weak organic bases (their dissociation constants range from 10^{-9} to 10^{-14}), it is difficult to determine them by neutralization in an aqueous medium. This is why the State Pharmacopoeia recommends, for example for caffeine, non-aqueous titration in a medium of protogenic (acidic) solvents such as anhydrous acetic acid.

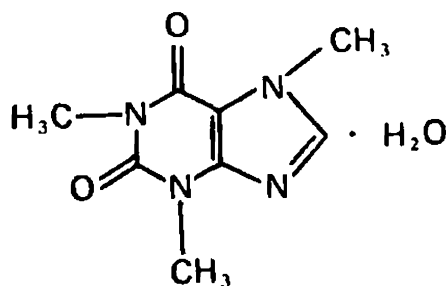
The acidic properties induced by the free imino group in the theobromine and theophylline molecules also allow non-aqueous titration to be used for their determination, but in a medium of protophilic (basic) solvents such as pyridine and dimethylformamide. This method is not an official one, however.

Spectrophotometry in the ultraviolet region can also be employed for the quantitative determination of the purine alkaloids. The double bonds in their molecules can cause resonance, which is why these substances absorb ultraviolet radiation. Purines produce one intensive band below 220 nm and another one at 272 nm, but they all have an identical peak and absorption intensity, therefore spectrophotometry in the ultraviolet region is a group method.

Other methods are also used for the quantitative determination of the purine alkaloids depending on the individual nature of each drug.

Caffeine (*Coffeinum*)

1,3,7-Trimethylxanthine



M.m. 212.21

M.m. 194.19 (anhydrous)

The main natural source of caffeine in the Soviet Union is tea production residues (tea dust, leaf trimmings, and tea leaves not suitable for food purposes). Caffeine is also contained in coffee seeds. At present, cheaper and more available synthetic and semisynthetic methods described above are used for the production of caffeine.

Caffeine forms white silky acicular crystals with a slightly bitter taste. It weathers in the air. It dissolves well in hot water and chloroform, and sparingly in cold water, benzene, and alcohol. It dissolves very poorly in ether.

Caffeine is a weak base. Its salts with mineral acids do not practically exist because they readily hydrolyze.

To identify caffeine, the murexide test and reactions of precipitation with the group alkaloid reagents are employed. It should be noted that these reactions have a number of distinctions for caffeine. For example, the latter is not precipitated by Mayer's reagent ($\text{HgI}_2 \cdot 2\text{KI}$), and yields a precipitate only in an acidic medium with an iodine solution. This precipitate has a brown colour and is a periodide: $\text{C}_8\text{H}_{10}\text{N}_4\text{O}_2 \cdot \text{HI} \cdot \text{I}_4$.

Unlike some other alkaloids, caffeine forms a white precipitate with a tannin solution that dissolves in an excess of the reagent.

The last two reactions, being the most specific for caffeine, are recommended by the State Pharmacopoeia.

The content of the drug is determined by non-aqueous titration in a medium of protogenic solvents (glacial acetic acid, acetic anhydride).

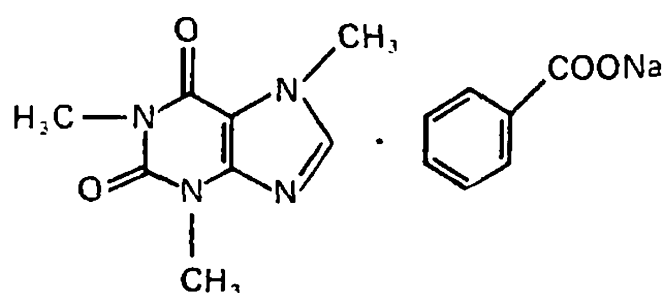
The ability of caffeine to form periodides with an iodine solution in an acidic medium can also be used for its quantitative determination. An excess of a standard iodine solution is added to a weighed sample of caffeine acidified with sulphuric acid, and a periodide precipitate forms. The excess iodine is titrated with a sodium thiosulphate solution (the official method).

Spectrophotometry in the ultraviolet region can also be used for the quantitative determination of caffeine.

Caffeine is administered as a stimulator of the central nervous system and a cardiotonic. The stimulating action of caffeine increases the mental and physical capacity for work, but its use in large doses results in exhaustion of the nerve cells.

The drug is dispensed in powders. It should be stored in well closed containers. It is listed in Group B.

Caffeine and Sodium Benzoate (*Coffeinum-natrii benzoas*)



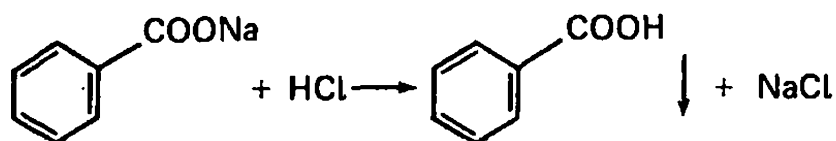
$C_{15}H_{15}N_4NaO_4$

M.m. 339.32

This drug is produced by mixing aqueous solutions of sodium benzoate and caffeine. The resulting transparent solution is evaporated until a dry powder forms.

The drug is a white powder with a slightly bitter taste. It dissolves readily in water and sparingly in alcohol. It gives reactions typical of caffeine. Among the reactions distinguishing this drug from caffeine are those for benzoic acid, namely, a pinkish-yellow precipitate forms with an iron(III) chloride solution. The sodium ion Na^+ is determined by its typical reactions.

The quantitative analysis of the drug is performed in two steps: (1) the amount of caffeine is determined iodimetrically after a weighed sample of the drug is acidified by an acid and the excess of a standard iodine solution is added; the amount of caffeine in the dry substance must be at least 38 and at most 40%; (2) the amount of sodium benzoate is determined in another weighed sample by neutralization; titration is performed in the presence of ether which extracts the evolving benzoic acid:



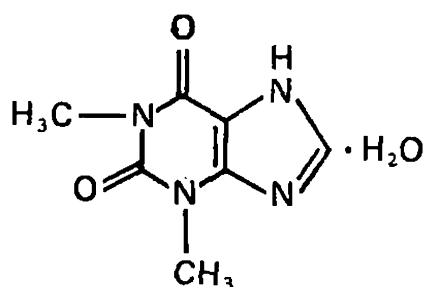
The amount of benzoic acid in the drug should be at least 58 and at most 62%.

Caffeine and sodium benzoate has the same indications for its administration as caffeine alone.

It is dispensed in 0.1- and 0.2-g powders and tablets, and also in ampoules in the form of 10% and 20% solutions.

The drug should be stored in well closed containers. It is listed in Group B.

Theophylline (*Theophyllinum*)
1,3-Dimethylxanthine



$C_7H_8N_4O_2 \cdot H_2O$

M.m. 198.18

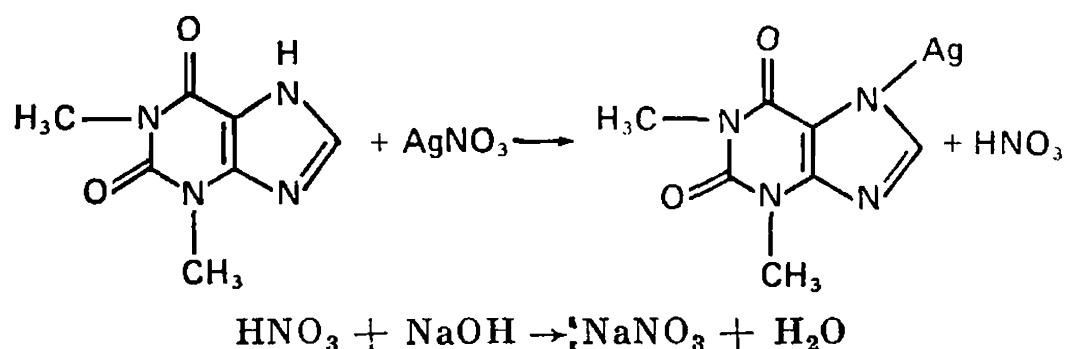
Theophylline is contained in tea leaves and coffee seeds. At present it is produced synthetically. Theophylline is a white crystalline powder with a bitter taste. It dissolves sparingly in cold water and readily in hot water. It is soluble in acids and alkalies (an amphoteric compound). Unlike caffeine and theobromine, theophylline dissolves in an ammonia solution because its acidic properties are more pronounced than those of theobromine.

Theophylline, like the other alkaloids of the purine series, gives a positive murexide test. It yields salts with metals owing to the acidic properties of the hydrogen of the imide group in position 7. The most typical of them are the silver and cobalt salts.

With cobalt salts, theophylline forms a white precipitate of a complex salt having a pinkish tint (a distinction from theobromine, which forms a salt of a different colour).

Unlike the other alkaloids of the purine series, theophylline gives a stable green colour with an alkaline solution of sodium nitroprusside.

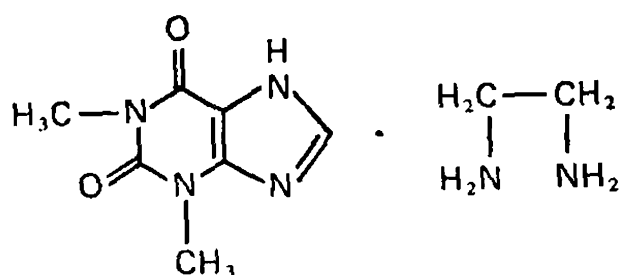
The content of theophylline in the drug is determined indirectly by neutralization of the nitric acid that forms together with the silver salt (the official method):



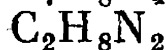
Theophylline has a spasmolytic, vasodilating, and diuretic action, and relieves bronchial spasms. It is dispensed in the form of 0.1- and 0.2-g powders and suppositories.

It should be stored in well closed containers protecting it from the action of light. It is listed in Group B.

Euphylline (*Euphyllinum*)
Theophylline with 1,2-ethylenediamine



M.m. 180.17



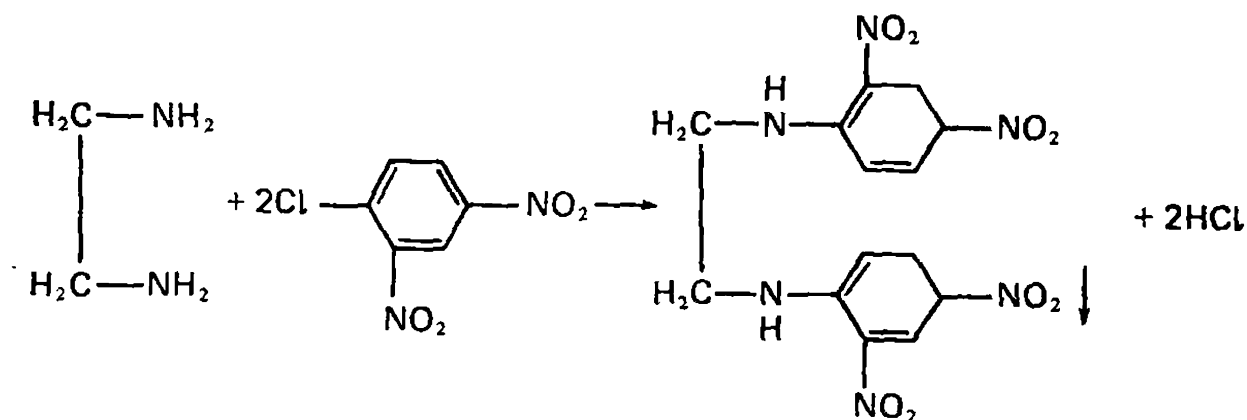
M.m. 60.10

Euphylline (aminophylline, thiophyllamine) was obtained when seeking for soluble theophylline preparations. It is a salt of theophylline with the organic base ethylenediamine and is obtained at the expense of the acidic properties of theophylline.

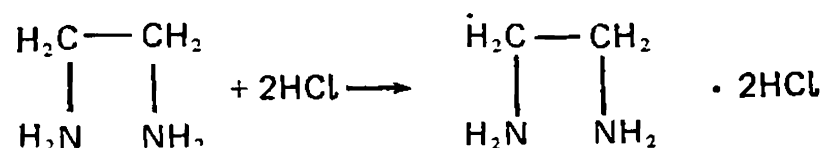
Euphylline is a white crystalline powder, sometimes with a yellowish tint, having a weak smell of ammonia. It is soluble in water. Its aqueous solutions have an alkaline reaction and a smell of ammonia. It absorbs carbon dioxide in the air, and its solubility diminishes. The drug is identified by:

- (a) the murexide test (the purine ring);
- (b) the formation of a bright violet complex when the drug is reacted with a copper sulphate solution (ethylenediamine);
- (c) the melting point of the theophylline separated after the ethylenediamine is neutralized with hydrochloric acid; the melting point of the precipitated theophylline base should be 269-274 °C.

In addition to the official reactions, euphylline can be confirmed by its reaction with 2,4-dinitrochlorobenzene. A yellow precipitate forms (a reaction for ethylenediamine):



According to the official requirements, in the quantitative analysis of euphylline, the theophylline content is determined indirectly by neutralization after drying and boiling the drug for the removal of ethylenediamine. The content of anhydrous theophylline in the drug should be 80-85%. The amount of ethylenediamine in another sample is determined by neutralization:



The drug should contain 14-18% of ethylenediamine.

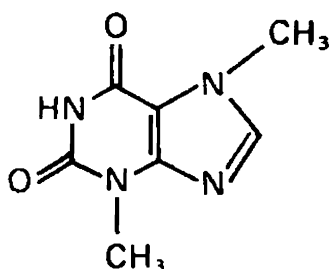
Euphylline, like theophylline, has a vasodilating and diuretic action. It is administered in bronchial asthma and angina pectoris.

It is taken orally in doses of 0.1-0.2 g, intravenously (2.4% solution in glucose), and intramuscularly (12% solution). It is dispensed in powders, tablets, and in ampoules.

Since euphylline rapidly absorbs carbon dioxide from the air, it should be stored in well closed jars in a place protected from light. It is listed in Group B.

Theobromine (*Theobrominum*)

3,7-Dimethylxanthine



$\text{C}_7\text{H}_8\text{N}_4\text{O}_2$

M.m. 180.17

Theobromine is a white crystalline powder with a bitter taste. It dissolves sparingly in water and still less in organic solvents. Being an amphoteric substance, it is soluble in alkalies and acids. It gives a positive murexide test. Its silver salt differs from those of caffeine and theophylline (it is a gelatin-like precipitate that liquefies when heated and again solidifies when cooled). Unlike caffeine and theophylline, it produces a grayish-blue precipitate in a reaction with cobalt chloride.

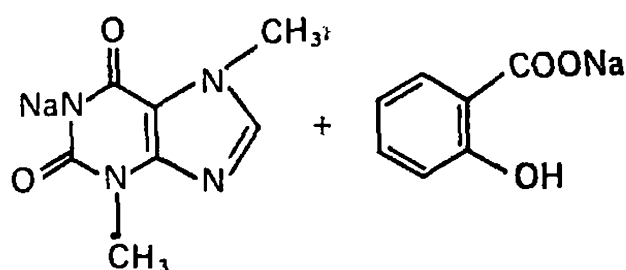
The content of the drug is determined, like that of theophylline, indirectly by neutralization.

It is employed as a diuretic and also as a stimulator of cardiac activity in spasms of the cardiovascular system and oedemae.

It is dispensed in 0.25-g powders and tablets. It is listed in Group B.

Themisal (*Themisalum*)

Sodium theobromine and sodium salicylate



$C_7H_7N_4NaO_2$

M.m. 202.15

$C_7H_5NaO_3$

M.m. 160.11

Themisal (theobromine sodium salicylate, salnabrom, theobromsal) is a mixture of sodium theobromine and sodium salicylate in molecular proportions. It is a white powder readily soluble in water and insoluble in ether and chloroform. An aqueous solution exhibits an alkaline reaction to phenolphthalein. It is hygroscopic.

In addition to the identification reactions for theobromine (the murexide test, etc.), reactions for sodium salicylate are performed:

(a) with an iron(III) chloride solution; after acidification of the drug with acetic acid, a violet colour appears (State Pharmacopoeia);

(b) with a copper sulphate solution; an emerald green colour of the solution is observed.

The quantitative analysis of the drug consists in determining:

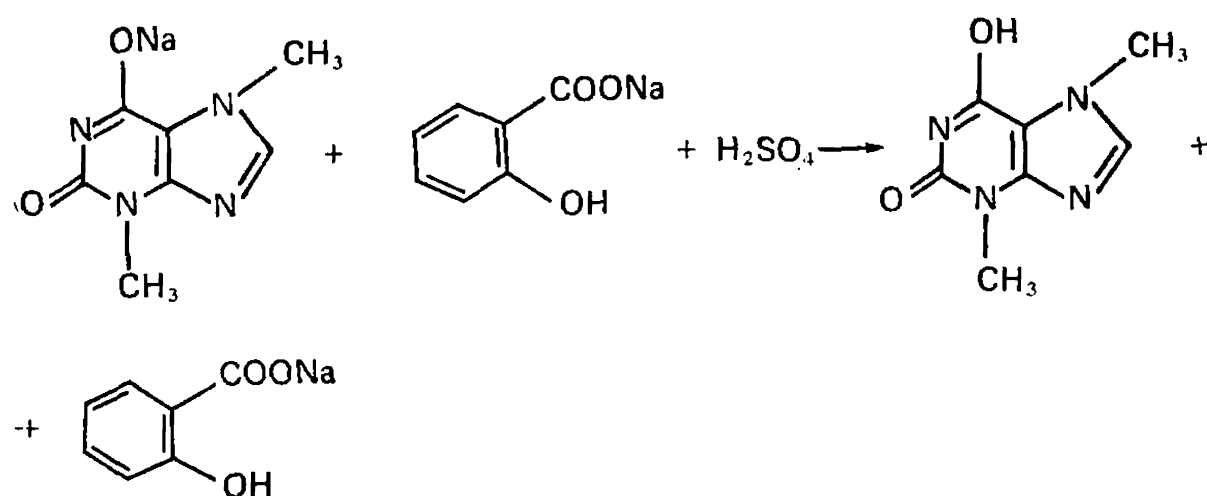
(1) the sodium other than that in the sodium salicylate, its content in the drug should be at least 6%;

(2) theobromine (at least 45%);

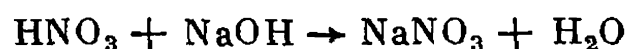
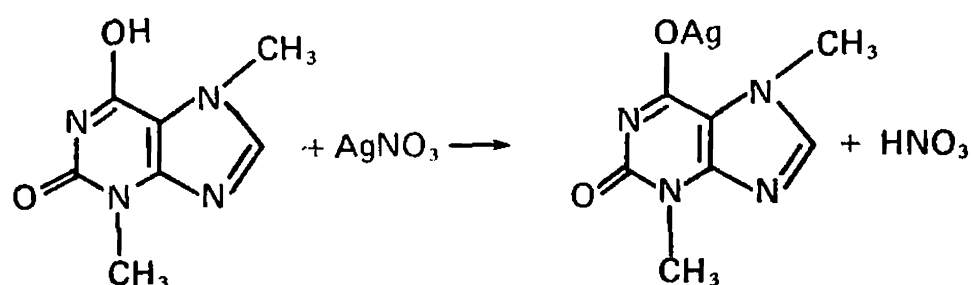
(3) sodium salicylate (at least 41%).

The quantitative determination of the unbound sodium is performed by neutralization. A weighed sample of the drug is dissolved in hot water, and a definite amount of a standard solution of an acid (H_2SO_4) is added in excess. The solution is boiled and the excess of the acid is titrated with an alkali (NaOH) using a phenol red indicator. The sodium salicylate under these conditions (without ether)

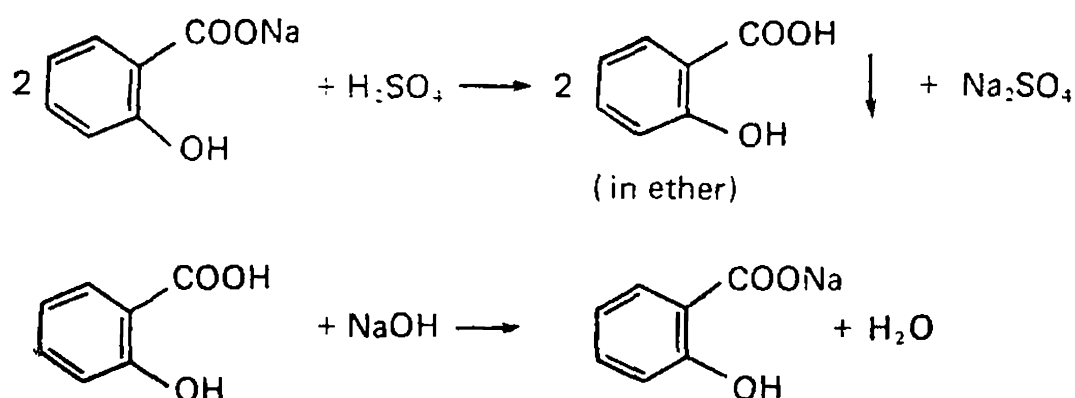
is not titrated:



After titration of the excess sulphuric acid, a standard solution of silver nitrate is added, and the evolved nitric acid is titrated with an alkali using a phenol red indicator (determination of the theobromine):



After the determination of the theobromine, the liquid is evaporated to a definite volume and acidified with dilute sulphuric acid. The evolving salicylic acid is extracted with ether, and the latter is distilled off. The residue is dissolved in a mixture of alcohol and water and titrated with a sodium hydroxide solution using a phenol red indicator (determination of the sodium salicylate):



Themisal, like theobromine, is a diuretic and vasodilating agent. It is dispensed in the form of a powder. It is prescribed chiefly in mixtures.

Since the drug is hygroscopic, it should be stored in well closed jars in a dry place. When moistened, the drug decomposes into sodium theobromine and sodium salicylate.

REVIEW QUESTIONS

1. Which compounds are called alkaloids?
2. What properties do alkaloids have?
3. What are the basic properties of alkaloids due to?
4. What alkaloid properties are their group reactions based on?
5. What underlies the chemical classification of the alkaloids?
6. Which heterocycles are contained in the tropane nucleus?
7. What is atropine from the chemical viewpoint?
8. What is the presence of two optical isomers and a racemate in atropine due to?
9. What properties of atropine sulphate is Vitali's reaction based on?
10. What underlies the use of acid-base titration in non-aqueous media for the quantitative determination of atropine sulphate? What is the advantage of this method?
11. Explain the use of photolorimetry in the determination of atropine sulphate.
12. Can the content of atropine sulphate be determined by neutralization relative to the acid residue?
13. What is scopolamine hydrobromide from the chemical viewpoint?
14. Why is Vitali's reaction positive for scopolamine?
15. What nucleus does the quinine molecule contain?
16. Describe the quinuclidine nucleus.
17. What are the features of quinine as a base?
18. What salts can quinine form?
19. Explain when quinine produces acid salts and when it produces neutral ones.
20. Why does the nitrogen of the quinuclidine nucleus have stronger basic properties?
21. How can quinine hydrochloride be distinguished from quinine dihydrochloride?
22. What properties of papaverine are used in its identification reaction?
23. Explain why morphine is a strong tertiary base.
24. What underlies the ability of morphine to form an azo dye?
25. Can morphine hydrochloride be determined quantitatively by neutralization?
26. Why is apomorphine hydrochloride readily oxidized?
27. What property of apomorphine underlies its identification reaction?
28. What is promedol (trimeperidine) from the chemical viewpoint?
29. Why does codeine react with an iron(III) chloride solution after saponification of the methoxy group?
30. How can one explain the ability of the codeine base to form salts?
31. What is reserpine from the chemical viewpoint?
32. What is pilocarpine in a chemical respect?
33. What is the optical activity of pilocarpine due to?
34. What rings does the purine nucleus consist of?
35. What are the basic properties of caffeine and the other purine derivatives due to?

36. Why are theobromine and theophylline amphoteric substances?
37. Explain the ability of caffeine to form complexes.
38. Explain the ability of theobromine and theophylline to form silver and cobalt salts.
39. What is the essence of the murexide test?
40. Under what conditions must themisal be stored?

PRACTICAL LESSON

Analysis of Quinine Sulphate

1. Dissolve 0.02 g of the drug in 5 ml of water and perform identification reactions.

(a) to 1 ml of the drug solution add bromine water until a weakly yellow colour appears, and then add an ammonium hydroxide solution; a green colour appears;

(b) add two or three drops of sulphuric acid to 2 ml of the drug solution; a light blue fluorescence appears;

(c) add two drops of a barium chloride solution to 1 ml of the drug solution; a white precipitate forms.

Write the equations of the chemical reactions.

2. Conduct a quantitative determination.

Transfer a sample of the drug with a mass of 0.05 g into a flask for titration and dissolve it in 10 ml of hot water, cool the solution, add 1 ml of chloroform, three drops of phenolphthalein, and titrate with a 0.1 *N* sodium hydroxide solution until a pink colour appears. Name the method used. Write the equation of the chemical reaction.

3. Calculate the quinine sulphate content in the drug in per cent by formula (1.1):

$$X = \frac{VKT}{a} \times 100 = \frac{VK \times 0.03915}{0.05} \times 100$$

where *V* is the volume of the 0.1 *N* sodium hydroxide solution, ml, *T* = 0.03915 g/ml, and *a* is the mass of the drug, g.

The State Pharmacopoeia requires that the drug contain at least 99.5% of $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$.

4. Compare the result obtained with the pharmacopoeial one and conclude whether the drug meets the requirements of the State Pharmacopoeia.

Analysis of a Mixture with Codeine Phosphate

1. Write the prescription in Latin:

Tincture of thermopsis 0.6-200.0 (g)

Codeine phosphate 0.2 (g)

Dispense. Indicate: 1 tablespoon 3 times a day.

2. Perform a quantitative determination. Transfer 10 ml of the mixture with a pipette into a flask for titration, add 1 ml of alcohol, and titrate with a 0.1 *N* sodium hydroxide solution until a pink colour appears (using phenolphthalein as the indicator). Write the equation of the chemical reaction.

3. Calculate the content of codeine phosphate in the mixture in grammes by formula (1.3):

$$X = \frac{VK Tb}{a} = \frac{VK \times 0.0212 \times 200}{10.0}$$

where V is the volume of the 0.1 N sodium hydroxide solution, ml, $T = 0.0212$ g/ml (relative to aqueous codeine phosphate), a is the volume of the mixture taken for titration, ml, and b is the total volume of the mixture, ml.

4. Compare the result obtained with the prescription and conclude whether the mixture may be released to a patient.

5. Propose identification reactions for codeine phosphate. Write the equations of the chemical reactions.

Analysis of a 10% Caffeine Solution ("Concentrate")

1. Write the equations of the chemical reactions of caffeine identification after your instructor has performed the identification reactions.

2. Perform a quantitative determination (by iodimetry). Place 5 ml of the solution into a 100-ml measuring flask, add 5 ml of a 2 N sulphuric acid solution and 15 ml of a 0.1 N iodine solution (from a burette). Add water up to the mark, thoroughly agitate the mixture, and let it stand for 15 minutes. Rapidly filter the solution through a cotton wool filter into a flask. Titrate 10 ml of the filtrate with a 0.1 N sodium thiosulphate solution until the solution loses its colour. Write the equation of the chemical reaction.

3. Evaluate the caffeine content in the solution in per cent by formulas (1.4) and (1.2):

$$X = \frac{(V_0 K_0 - VK) TV_1}{aV_2} \times 100 = \frac{(15.00 \times K_0 - VK) \times 0.0053 \times 100 \times 100}{5.0 \times 10.0}$$

where V_0 is the volume of the 0.1 N iodine solution, ml, V is the volume of the 0.1 N sodium thiosulphate solution, ml, K_0 is the correction factor for the 0.1 N iodine solution, K is the same for the 0.1 N sodium thiosulphate solution, $T = 0.0053$ g/ml (relative to aqueous caffeine), a is the volume of the drug taken for the determination, ml, V_1 is the volume of the drug solution after the first dilution, ml, and V_2 is the volume of the aliquot part of the diluted solution, ml.

4. Compare your result with the required concentration and arrive at the corresponding conclusion.

Analysis of Caffeine and Sodium Benzoate

1. Perform identification reactions:

(a) dissolve 0.01 g of the drug in 3 ml of water and add one drop of an iron(III) chloride solution; a yellow-pink precipitate forms;

(b) introduce a minute particle of the drug into a colourless burner flame; the colour will turn yellow.

Write the equations of the chemical reactions.

2. Conduct a quantitative determination (by neutralization). Dissolve 0.05 g of the drug in 5 ml of water, add 3 ml of ether, three drops of methyl orange, one drop of methylene blue, and titrate with a 0.1 N hydrochloric acid solution until an intensive violet colour appears. Write the equations of the chemical reactions.

3. Compute the content of caffeine and sodium benzoate in the drug in per cent by formula (1.1):

$$X = \frac{VKT}{a} \times 100 = \frac{VK \times 0.0338}{0.05} \times 100$$

where V is the volume of the 0.1 N hydrochloric acid solution, ml, $T = 0.0338$ g/ml, and a is the mass taken for the determination, g.

The State Pharmacopoeia requires that the content of $C_{15}H_{15}N_4NaO_4$ in the drug be at least 98.0%.

4. Compare your result with the official requirements and arrive at the corresponding conclusion.

Analysis of Theobromine (Problem Solving Research Method)

1. Write the English, Latin, and chemical name of the preparation 3,7-dimethylxanthine in your notebook.

Proceeding from the chemical name, depict the formula of theobromine graphically.

Study the physical properties of the preparation, namely, the colour, odour, and taste of the crystals. Test the solubility in water and in 95% alcohol; for this purpose, shake 0.05 g of the preparation with 1 ml of distilled water or 1 ml of alcohol. Test the solubility in dilute acids and alkalies; for this purpose, dissolve 0.05 g of the preparation in 1-2 ml of dilute hydrochloric acid (a 6 N solution) with shaking and then in 1 ml of a 2 N sodium hydroxide solution. Enter your observations in your notebook. Substantiate them.

2. Perform identification reactions.

(a) What reaction can be used to confirm that theobromine belongs to the alkaloids of the purine series? Disclose the chemism of this process.

Perform the indicated reaction as follows: put 0.05 g of theobromine into a porcelain bowl, add three drops of perhydrol, then three drops of dilute hydrochloric acid, and evaporate the solution in a water bath till dry. Wet the residue with one or two drops of an ammonium hydroxide solution. What do you observe? Write your observations in your notebook.

(b) Perform the following reaction: to 0.1 g of the preparation add 2 ml of a 0.1 N sodium hydroxide solution, agitate the mixture for two minutes and filter it into another test tube. Add three drops of a 2% cobalt chloride solution to the filtrate and shake it for one or two minutes. Write what you observe in your notebook. Explain the chemical essence of the occurring process.

(c) Dissolve 0.05 g of theobromine in 1 ml of a 2 N sodium hydroxide solution, add 10 drops of an ammonium hydroxide solution and eight drops of a 5% silver nitrate solution (add the latter by drops and shake the mixture vigorously after each drop up to complete dissolution of the initially formed brown silver oxide precipitate).

Write what you observe in your notebook. Explain the chemical essence of the occurring process. Write the equation of the chemical reaction.

3. Conduct a quantitative analysis.

Proceeding from the structure and properties of theobromine, propose a method for its quantitative determination. Write down the chemism of the process.

Conduct a quantitative determination using the following procedure: put about 0.1 g of theobromine (an exact mass) into a 100-ml conical flask, add 30 ml of distilled water and boil with an inserted funnel up to complete dissolution of the preparation. Add 10 ml of a 0.1 N silver nitrate solution (via a burette) to the hot solution, agitate the mixture, cool it to room temperature, add 15 drops of an indicator (a 0.1% phenol red solution), and titrate with a sodium hydroxide solution up to the appearance of a violet-red colour.

Evaluate the theobromine content in the preparation in per cent.

What storage conditions can you propose for the given preparation? The highest single oral dose is 1.0 g, and the highest daily oral dose is 3.0 g.

The preparation is employed as a spasmolytic (vasodilating, bronchodilating) and diuretic drug.

Chapter 29. Glycides and Their Derivatives

(Independent Work. Problem Solving Research Method)

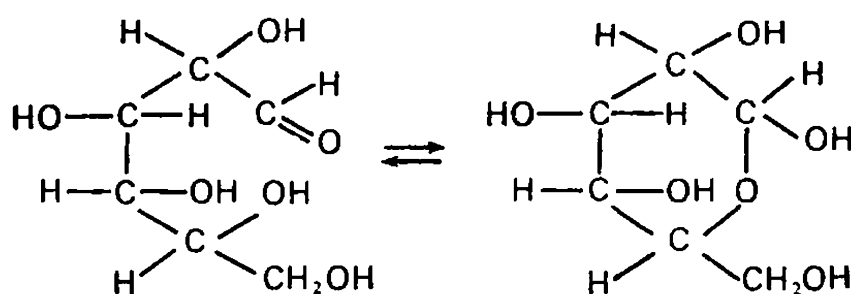
I. A general characteristic of glycides*.

What groups of substances relate to glycides?

Give the classifications of glycides:

- (a) by their ability to hydrolyze,
- (b) by the number of carbon atoms in a molecule,
- (c) by the presence of an aldehyde or keto group.

What functional groups do the glycides contain?



What reactions will glycides participate in owing to their alcohol hydroxyl groups?

What kind of isomers are listed in the table (the latter is prepared in good time by the students under the guidance of their instructor)?

The glycides are optically active substances.

II. Write the Latin name and the formula of glucose (see the State Pharmacopoeia).

Which glycides does glucose relate to in accordance with the classification?

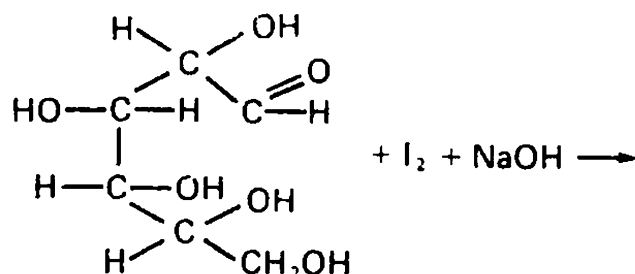
Where is glucose encountered in nature? How can it be produced?

Characterize the physical properties of glucose (State Pharmacopoeia).

How can glucose be identified (State Pharmacopoeia)? Which functional group is the reaction due to? Write the equation.

What other reaction can be used to identify glucose?

Quantitative determination:



* Preliminarily repeat the topic "Carbohydrates" from the course in organic chemistry.

Name the method of quantitative analysis, draw up its procedure, complete the reaction equations, and explain the mechanism.

What physicochemical methods of analysis can be used for the quantitative determination of glucose?

How should glucose be stored?

What purpose is glucose employed for?

III. Write the Latin name and formula of calcium gluconate (see the State Pharmacopoeia).

Write the structural formula of the drug.

What is this drug as regards its chemical structure?

Which substances can be used to produce calcium gluconate?

How can calcium gluconate be produced?

Characterize its physical properties (State Pharmacopoeia).

Write the equation of the reaction for the calcium cation.

How can the drug be determined quantitatively (State Pharmacopoeia)? Analyse the chemism of the reaction.

How should the drug be stored (State Pharmacopoeia)?

What is the drug used for (State Pharmacopoeia)?

PRACTICAL LESSON

Analysis of Calcium Gluconate

1. Write the Latin name of the drug. Proceeding from the name, write the formula of the drug. What is calcium gluconate from the chemical viewpoint?

Study the physical properties of the drug—its colour and odour. Test its solubility in water and alcohol; to do this, dissolve about 0.05 g of the drug in 3 ml of water while shaking, and then heat the mixture. Dissolve about 0.05 g of the drug in 2 ml of alcohol and shake the solution. Comment on the results.

2. Conduct an identification test:

(a) wet 0.05 g of the drug with hydrochloric acid and introduce it into a colourless burner flame. Explain what causes the colour of the flame to change.

Dissolve 0.05 g of the drug in 2 ml of water:

(b) to a part of the obtained solution add 0.5 ml of an ammonium oxalate solution and agitate the mixture. What do you observe? Test the solubility of the obtained precipitate in hydrochloric and acetic acids. Compile the relevant reaction equations;

(c) to the remaining part of the drug solution add two drops of an iron(III) chloride solution. What do you observe?

3. Proceeding from the structure and properties of calcium gluconate, select a possible method for its quantitative determination. Perform a quantitative determination of the drug by the pharmacopoeial method: put about 0.1 g (an exactly weighed sample) of calcium gluconate into a 100-ml measuring flask, dissolve it in hot water, add water up to the mark, cool the mixture and thoroughly stir it. Next transfer 10 ml of the diluted solution into a flask for titration, add 5 ml of an ammonia buffer and three drops of an indicator (a solution of Acid Chrom Dark Blue) and titrate with a 0.05 M solution of Na-EDTA until a blue-violet colour appears.

Name the given method of quantitative determination. Compile the reaction equations, perform the calculations, and arrive at a conclusion on the analysis

results. $T = 0.022\ 45$. The State Pharmacopoeia tolerates a calcium gluconate content in the drug of at least 99.5% and most 103.0%.

Proceeding from the studied properties, recommend the conditions of storage of the drug.

Chapter 30. Vitamins

Vitamins are biologically active organic compounds of a diverse chemical nature. They enter an animal's or human's organism with the food, in small amounts, and play a major role as biocatalysts in metabolism. Both a lack and an excess of vitamins in an organism cause deep disturbances of various functions of the organism, the result being severe diseases.

When there is a lack of vitamins in an organism, diseases called hypovitaminoses develop. For example, an insufficiency of vitamin C may cause scurvy, an insufficiency of vitamin D may cause rickets (especially in children), an insufficiency of vitamin A—blindness, of vitamin B₁—polyneuritis, and so on.

Diseases associated with the absence of a vitamin in an organism are called avitaminoses.

An excess of vitamins in an organism leads to a disease known as hypervitaminosis. For example, when an organism contains an excess of vitamin K regulating the coagulation of the blood, thrombophlebitis sets in. It is a severe disease associated with clogging of the blood vessels.

To relieve phenomena of hypervitaminosis, vitamin inhibitors or antagonists called antivitamins are used. To date antagonists are known for almost all the vitamins, but there are only a few drugs among them.

The discovery of vitamins is associated with the name of the Russian physician N. Lunin, who back in 1880 in experiments with animals created a special diet for them and showed that for the normal life of an animal organism food is necessary that contains not only proteins, fats, carbohydrates, and mineral salts, but also other substances present in natural products. However, Lunin's work did not win recognition at that time, and only many years later did investigators return to this problem. In 1912, on the basis



N. Lunin (1853-1937)

of Lunin's work, the Polish biochemist K. Funk separated a physiologically active substance in the crystalline form from rice bran. This substance completely healed patients from polyneuritis ("beriberi").

After it had been established that the substance which Funk separated from rice bran contained nitrogen, he presumed that all the other substances whose absence in a diet cause avitaminosis contain nitrogen. He therefore proposed to call these substances **vitamins** (*vita* is the Latin for life + amine). But further studies showed that not all vitamins contain nitrogen, therefore the name of these substances is not completely accurate. It has been established that the molecules of vitamins contain a hydroxyl group (of a pheno, alcohol, or acidic nature). Vitamins are supplied to an organism in insignificant amounts with food. They combine with specific proteins to form enzyme systems.

Quite frequently, food contains substances that are chemically similar to a vitamin. During metabolism or photosynthesis, these substances transform into vitamins. Such substances are called **provitamins**. For example, the carotenoids contained in carrots have a structural part of vitamin A in their molecule. After getting into an organism, the carotenoids enter into reactions of oxidation and metabolism and are converted into vitamin A. Hence, carotenoids are provitamin A. Another example is sterines, which under the influence of ultraviolet radiation are converted into vitamin D and are thus provitamins of this vitamin.

To date, almost all the known vitamins, except a very few, are produced synthetically on a commercial scale. At the present stage of development of vitaminology, scientists are interested in the mechanism of vitamin action. It was established that vitamins become biocatalysts when a considerable part of the vitamins is converted in the cells of an organism into their active form—a co-enzyme. This opens the way for artificial synthesis of co-enzymes to be used in medicine instead of vitamins. This is especially important in disturbances of the intracellular biosynthesis of co-enzymes from vitamins. An example of the artificial creation of a co-enzyme is the synthetic co-carboxylase (thiamine pyrophosphate).

Great attention is being devoted to this field of research at present. Some co-enzyme drugs are already being produced by Soviet enterprises, namely, lipoic acid and its amide regulating lipid and carbohydrate metabolism in an organism, the mononucleotide of riboflavine (an ester of riboflavine and phosphoric acid) administered when there is a lack of vitamin B₂ in an organism and flavinate (a co-enzyme of vitamin B₂), and phosphatylamine (a co-enzyme of vitamin B₁).

Classification. Initially there was a letter classification of vitamins, i.e. the letters of the Latin alphabet were used to designate

vitamins as they were discovered. When the number of discovered vitamins began to grow, numerical subscripts were added to the letters, for example B₁, B₂, B₅, B₆, etc.

Since the letter classification reflects neither the biological nor chemical essence of vitamins, it was proposed to classify them by their physiological action, namely, vitamin A was given the name axerophthol because a lack of this vitamin in an organism causes xerophthalmia—an eye disease; vitamin E was given the name tocopherol (Gk *tokos* birth, and *pherein* to bear), etc.

But this classification does not make it possible to combine the constantly growing number of vitamins with a certain common feature into separate groups, which became extremely necessary.

In this connection, a physical classification was proposed, by which all the vitamins are divided into two large groups: soluble in fats (A, D, E, etc.) and soluble in water (vitamins of the B complex, folic acid, etc.).

As the chemical structure of vitamins was established, it became possible to classify vitamins according to their chemical structure.

In addition to the adopted chemical classification, however, to date the letter and physical classification of vitamins are encountered in a number of publications.

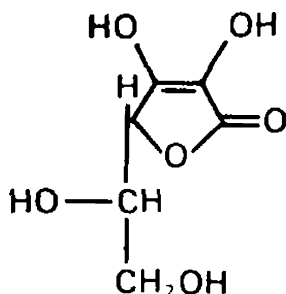
The chemical classification divides all vitamins into four main groups: 1. Vitamins of the aliphatic series. 2. Vitamins of the alicyclic series. 3. Vitamins of the aromatic series. 4. Vitamins of the heterocyclic series.

Each of these groups has subgroups combining vitamins in accordance with specific features of their chemical structure.

30.1. ALIPHATIC DERIVATIVES

Ascorbic Acid (Vitamin C) (*Acidum ascorbinicum*)

2,3-Dehydro-L-gulonic acid γ-lactone (3-Keto-L-gulofuranolactone)



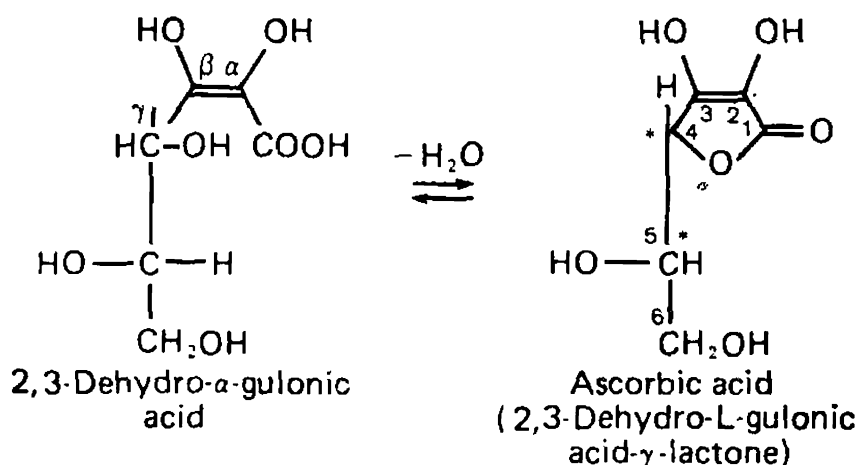
C₆H₈O₆

M.m. 176.13

Prior to 1912, it was not known that the severe disease scurvy was due to a lack of vitamin C, although already at the end of the 19th century the Russian physician V. Pashutin advanced the idea that scurvy appears owing to a lack in the organism of a very important substance. In 1922, N. Bessonov isolated from cabbage a crystal-

line substance healing scurvy, while in 1928 the Hungarian scientist A. Szent-Györgyi separated from the adrenal cortex a substance of an acidic nature with sharply pronounced reducing properties and a molecular mass of 176. Since this substance healed scurvy, it was called ascorbic acid (from the Latin *scorbut* scurvy).

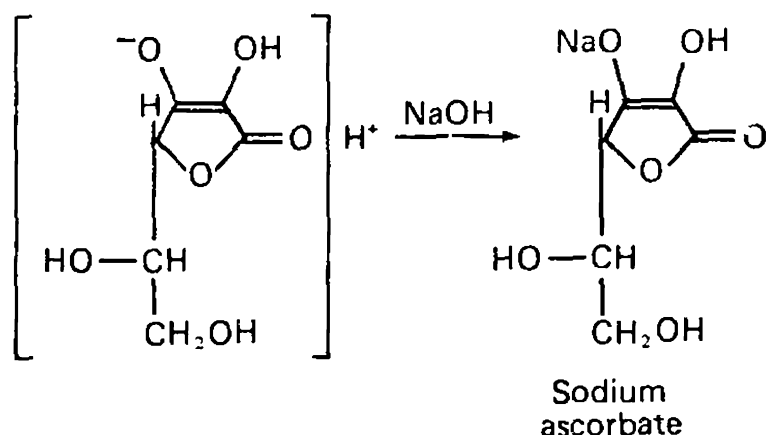
When determining the structure of ascorbic acid, it was established that the acid can form a tetramethyl ether, which points to the presence of four hydroxyl groups in its molecule. In the catalytic hydrogenation of ascorbic acid, one mole of hydrogen is absorbed, which confirms the presence of a double bond in its molecule. It was also established that the ascorbic acid molecule contains a lactone ring. All these data led to the conclusion that ascorbic acid is a γ -lactone of 2,3-dehydro-L-gulonic acid:



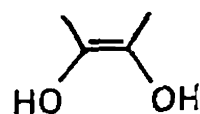
The synthesis of ascorbic acid in 1933 confirmed its structure. The acid is synthesized commercially from D-glucose, which is produced in large amounts when starch is decomposed by sulphuric acid.

The ascorbic acid molecule has two asymmetric carbon atoms (C-5 and C-6), which underlies the existence of four optical isomers; all of them have been produced synthetically.

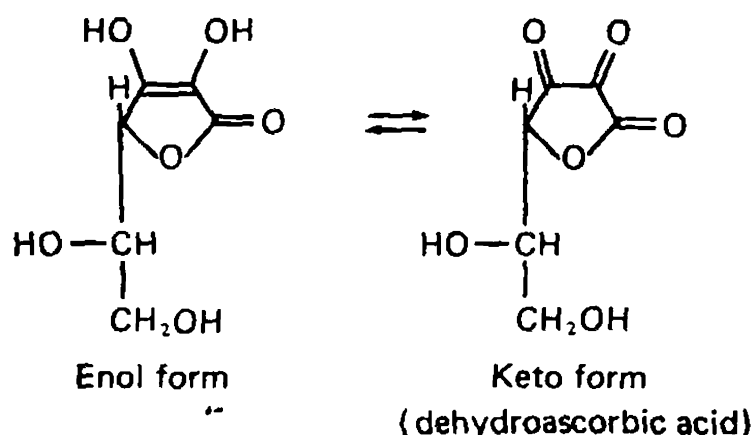
Ascorbic acid is a white crystalline powder with an acidic taste. It dissolves readily in water, is soluble in alcohol, and is insoluble in ether, benzene, and chloroform. Its melting point is 190-193 °C (with decomposition). Ascorbic acid behaves like a monobasic acid. Its acidic properties are due to the hydrogen of the hydroxyl group in position 3, and it is this hydrogen that forms salts:



The enediol group of the ascorbic acid molecule is responsible for its chemical properties and physiological activity:



Owing to the mobility of the hydrogen atoms of the enol hydroxyl groups, ascorbic acid is readily oxidized, and this can occur in two steps. The first oxidation step is a reversible process when the ascorbic acid is oxidized to dehydroascorbic acid (the keto form), which can be reduced again to ascorbic acid:

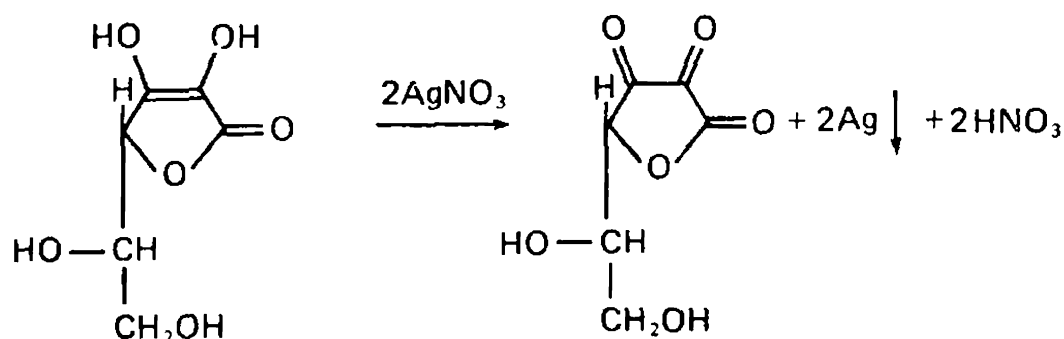


In the second step, the oxidation process in an aqueous medium can proceed further, up to the decomposition of the dehydroascorbic acid. This process is irreversible, hence the decomposition products cannot be converted again into ascorbic acid, and the physiological activity is lost.

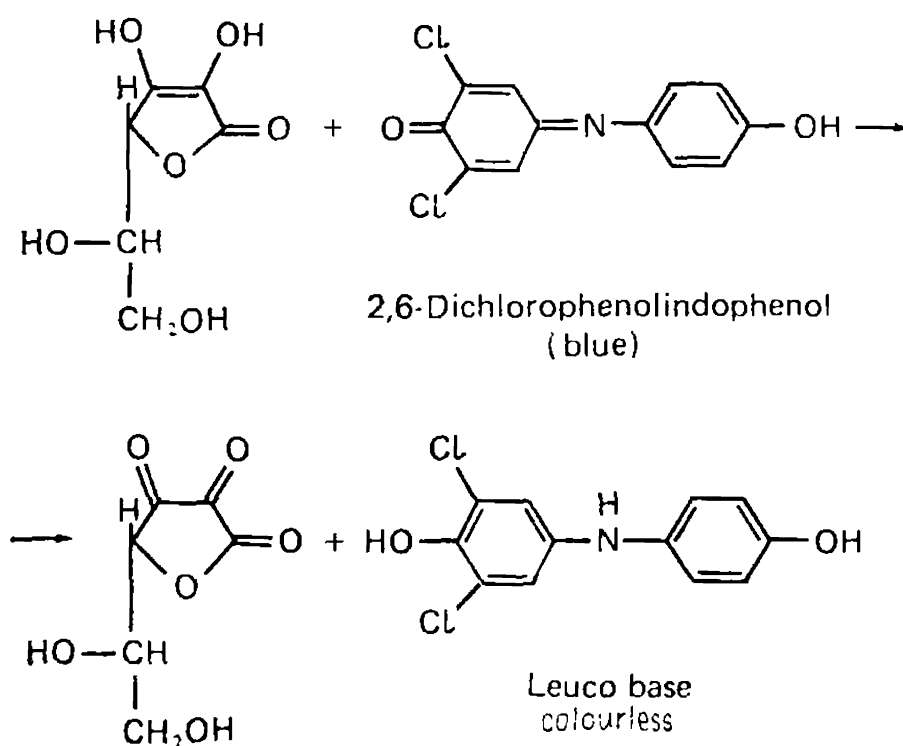
An important property for the manifestation of the physiological activity of ascorbic acid is its reversible oxidation to dehydroascorbic acid, i.e. the oxidation-reduction ability of ascorbic acid. In this case, it can be a donor, i.e. it donates two hydrogen atoms and is oxidized to the dehydro form, or can be an acceptor of hydrogen, which is attended by conversion to the enol form. Owing to the reversibility of these processes, ascorbic acid can be a carrier of hydrogen in enzyme systems and, consequently, participate in the oxidation-reduction processes in an organism. With a view to this important physiological role of ascorbic acid in the first oxidation step, various stabilizers are added to the acid when preparing its solutions for injections. An example of such stabilizers is sodium hydrogen sulphite. It is also necessary to provide the appropriate conditions for the storage of these solutions (the absence of light and no contact with metals, especially with salts of iron).

To identify ascorbic acid, its ability to participate in oxidation-reduction reactions is taken advantage of:

(a) when ascorbic acid is reacted with a silver nitrate solution, the silver is reduced (a dark precipitate); the acid itself is oxidized and transforms into the keto form:

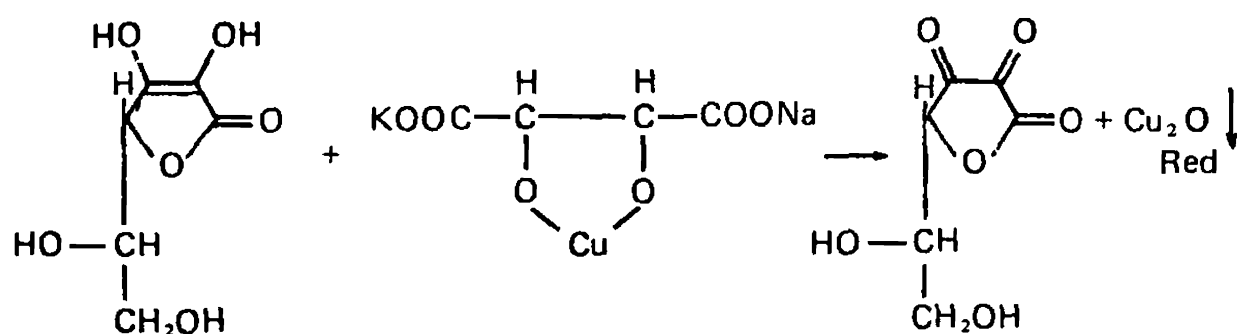


(b) when ascorbic acid is reacted with a solution of 2,6-dichlorophenolindophenol (coloured blue), the latter is reduced and transforms into the colourless leuco base:

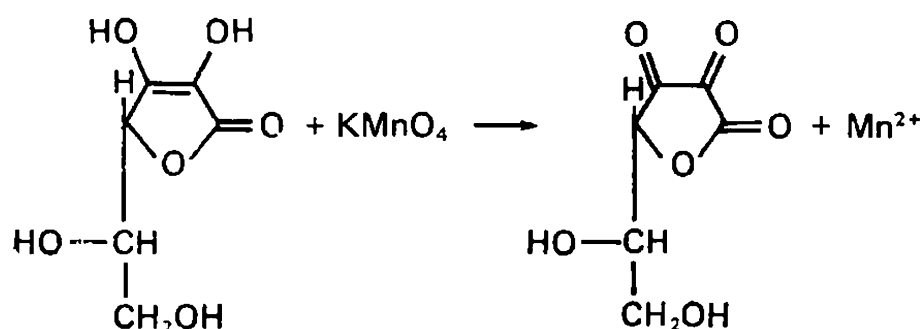


In addition to these two reactions recommended by the State Pharmacopoeia, many others can be cited that are based on the reducing properties of ascorbic acid:

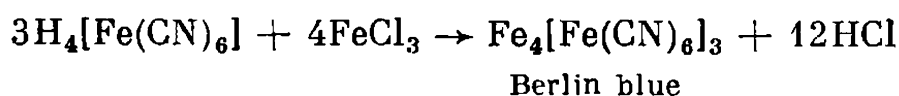
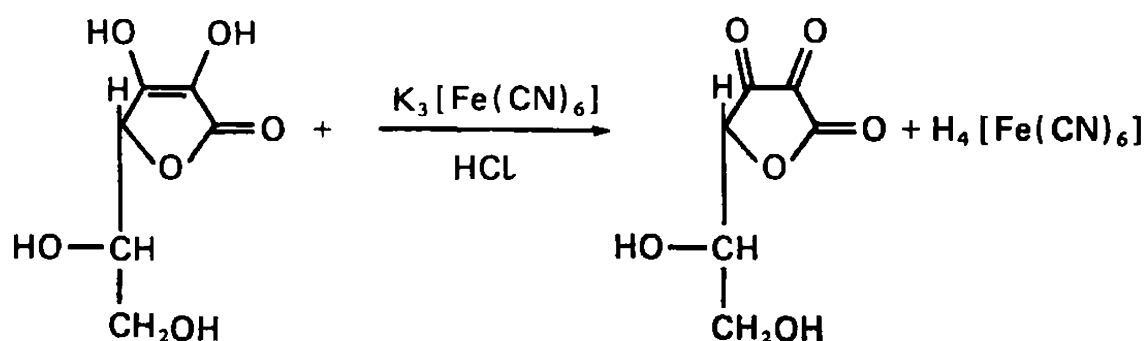
with Fehling's solution; copper(II) is reduced to red copper(I):



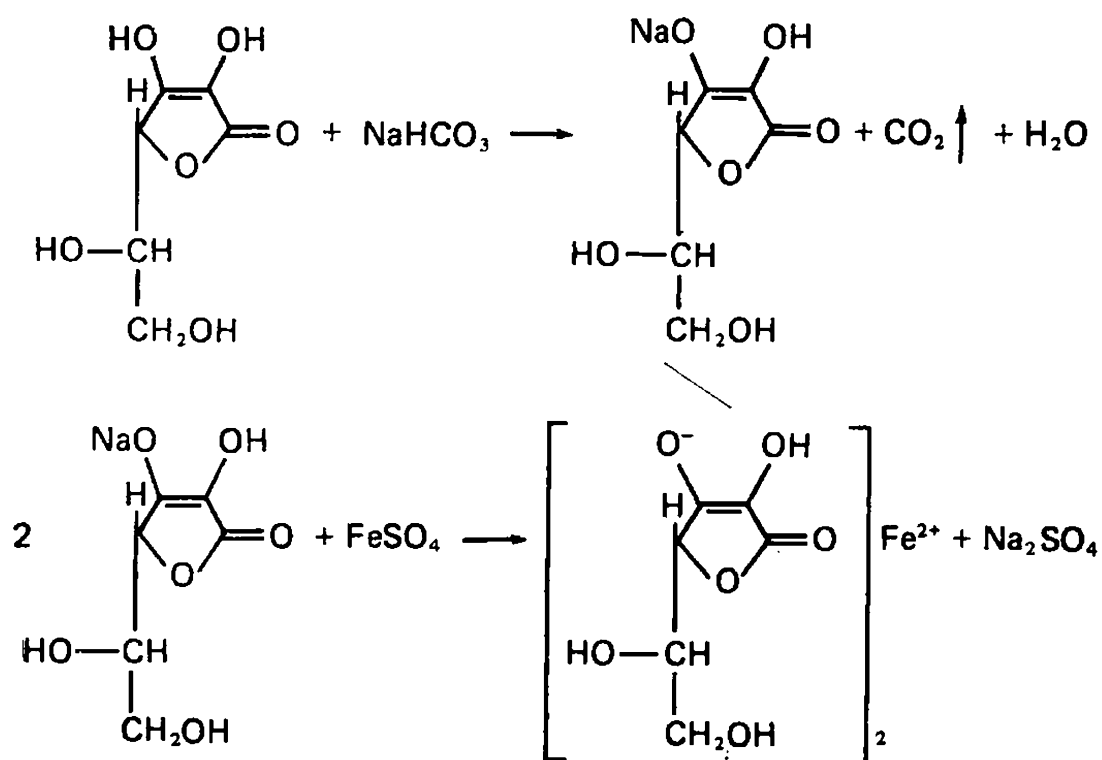
with a potassium permanganate solution; the solution loses its colour because of reduction of MnO_4^- to Mn^{2+} :



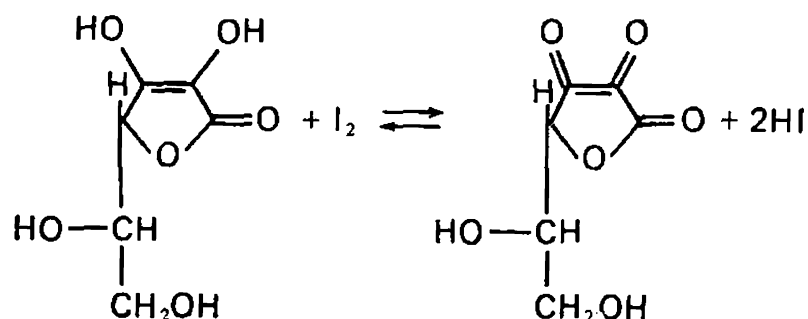
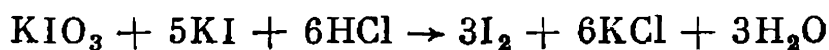
with potassium ferricyanide in the presence of dilute hydrochloric acid and with the following addition of iron(III) chloride; Berlin blue forms that colours the solution blue:



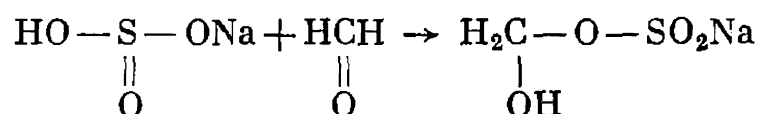
ascorbic acid forms violet iron ascorbate with an iron(II) salt after first being transformed into a sodium salt (by a reaction with sodium hydrogen carbonate):



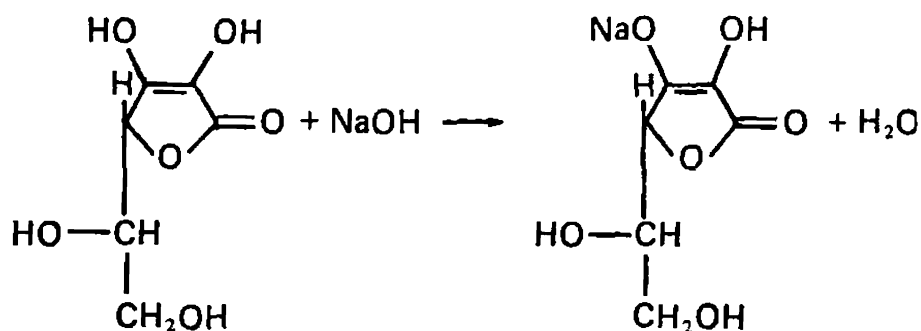
The quantitative determination of ascorbic acid is also based on its chemical properties. Iodimetry is the official method. Here a potassium iodate solution is the titrant. Titration is performed in the presence of potassium iodide and hydrochloric acid (starch is the indicator) until a stable blue colour appears:



The content of ascorbic acid in solutions is also determined iodimetrically, but here it must be remembered that ascorbic acid solutions contain a stabilizer—sodium hydrogen sulphite NaHSO_3 , which as a reducing agent can react with iodine. Therefore a formaldehyde solution (formalin) is preliminarily added to the ascorbic acid solution to bind the sodium hydrogen sulphite, and the iodine is thus used only to oxidize the ascorbic acid:



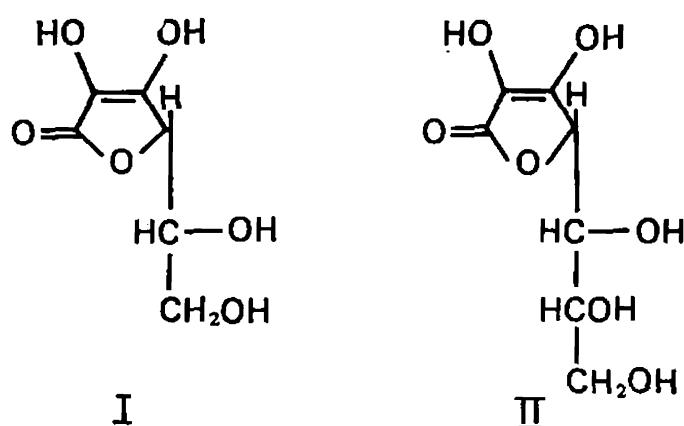
Ascorbic acid can also be determined quantitatively by neutralization as a monobasic acid:



A change in the structure of the ascorbic acid molecule leads either to a decrease in or a loss of its vitamin activity. The physiological activity of ascorbic acid is substantially lowered or completely lost when the number of carbon atoms in its molecule increases.

At present, over ten isomers and analogues of ascorbic acid are known that are its antagonists. Among the known antivitamin of ascorbic acid, the most potent are D-ascorbic acid (I) and D-glucoas-

corbic acid (II) whose molecule contains one more carbon atom than the ascorbic acid molecule:



Crystalline ascorbic acid is stable, but it rapidly oxidizes in aqueous solutions and loses its biological activity, especially in the air in the presence of traces of metals (owing to catalysis), and in an alkaline or acidic medium. The first indication of decomposition of ascorbic acid is the appearance of a yellow tint.

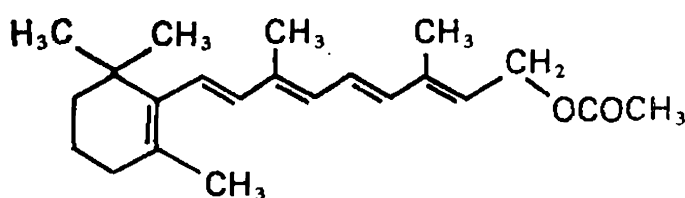
It is administered orally, intramuscularly, and intravenously. It is dispensed in the form of 0.05-g powders and tablets, and in ampoules containing 1 or 5 ml of a 5% solution.

Ascorbic acid is often prescribed in combination with glucose (tablets of ascorbic acid with glucose) or rutin (ascorutin). It is contained in polyvitamin drugs.

30.2. ALICYCLIC DERIVATIVES

RETINOLS (GROUP A VITAMINS)

Retinol Acetate (*Retinoli acetas*)



$C_{22}H_{32}O_2$

M.m. 328.50

It was considered for many years that the action of vitamin A is exhibited only by substances contained in products of an animal origin, chiefly in sea and fresh-water fish, and especially in cod liver. It is exactly from these natural sources that vitamin A was produced for a long time.

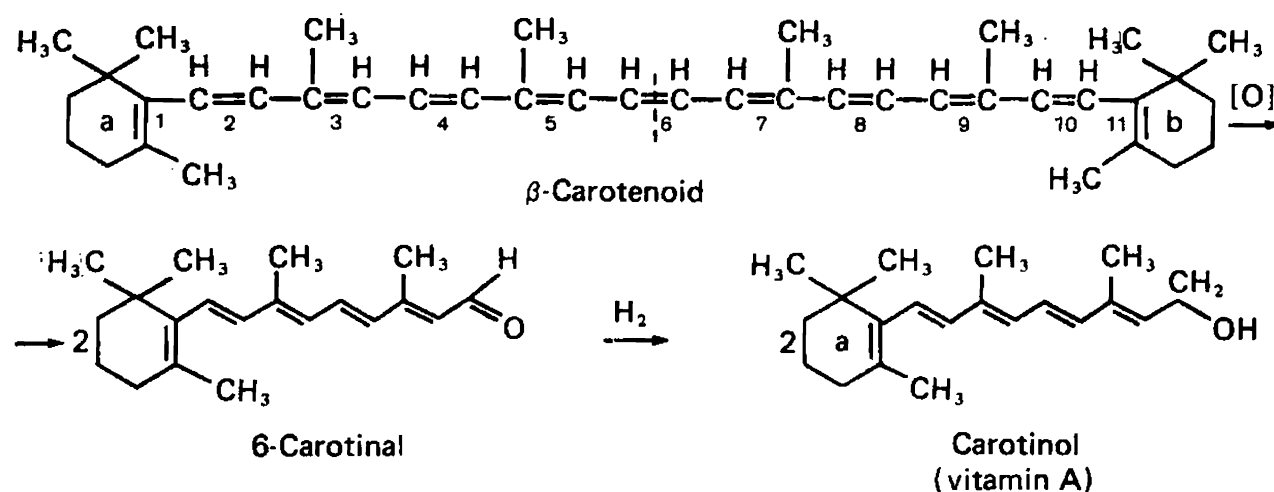
It was later established that some substances of a plant origin such as carotenes separated from carrots and turnips also have the

action of vitamin A. When they get into an organism, the carotenes are transformed by enzymes into vitamin A, consequently they are provitamins of vitamin A.

At present, this group of vitamins is called carotenoids in the international nomenclature. It includes the carotenes and the group of vitamins A (retinols).

Of the three main natural carotenes (α -, β -, and γ -carotenes), β -carotene has the highest physiological activity because it is oxidized and decomposed in an organism to form two molecules of vitamin A, whereas the other two carotenes can form only one molecule.

The oxidation of β -carotene can be shown schematically as follows:



The formulas show that β -carotene has two β -ionone rings (a and b); a vitamin A molecule has a similar ring. The carbon chain of β -carotene consists of 22 carbon atoms, four of them being in branched methyl groups. The system of conjugated double bonds in the carbon chain of the carotene molecule underlies its chemical transformation such as hydrogenation and oxidation.

Depending on the oxidizing agent, the carotene chain can break at one of the double bonds with the formation of an aldehyde (carotenal). The carbon polyene chain of the resulting aldehyde can have a various length depending on the double bond at which the chain was broken. The reduction of carotenals yields alcohols—carotenols.

If oxidation of carotene occurred at the sixth double bond of its molecule (as shown above), 6-carotinal is produced which when reduced forms the carotenol known as vitamin A.

Vitamin A is produced synthetically for medical purposes.

In its chemical structure, retinol is an unsaturated primary alcohol that can be oxidized to an aldehyde (carotenal) and can form esters with acids. The esters of retinol have a higher stability than retinol itself. The acetate (retinol acetate) has the highest physiological

activity, therefore it has been adopted as an international standard and is a pharmacopoeial drug.

Retinol acetate forms white or pale yellow crystals with a weak odour. It is soluble in alcohol, chloroform, ether, and fatty oils, and is virtually insoluble in water.

Retinol yields colour reactions with solutions of antimony(III) chloride, arsenic(III) chloride, and glycerin dichlorohydrin.

The official reaction is that with an antimony(III) chloride solution in chloroform. The product has a blue colour. The melting point of retinol acetate is 53-57 °C.

The quantitative determination of retinol acetate is based either on its reaction with a chloroform solution of antimony(III) chloride (the photolorimetric method) or on measurement of the absorption in the ultraviolet part of the spectrum of alcohol or chloroform solutions of the vitamin.

The State Pharmacopoeia recommends the spectrophotometric determination of retinol acetate in an alcohol solution. In this case, the optical density of an alcohol solution of the drug (prepared from an exactly weighed sample) is measured in a spectrophotometer in a cell with a layer thickness of 1 cm at a wavelength of 326 nm. The absorption peak corresponds to this wavelength. By comparing the magnitude of the absorptivity (extinction coefficient) a for the solution being tested with the absorptivity of a standard solution, one can calculate the content of retinol acetate by the relevant formula. Since retinol acetate can be readily oxidized, it is stored in ampoules sealed in a stream of nitrogen at a temperature not exceeding +5 °C.

Another pharmacopoeial preparation of retinol is a solution of retinol acetate in oil: *Solutio Retinoli acetatis oleosa* 3.44%, 6.88%, 8.60%.

A retinol acetate solution in oil is a transparent oily liquid ranging in colour from light yellow to dark yellow.

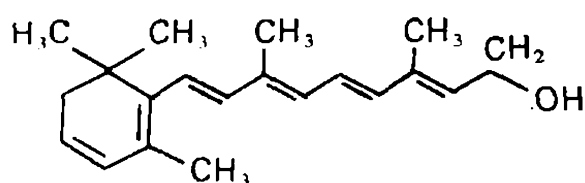
In addition to the reaction with an antimony(III) chloride solution, the State Pharmacopoeia recommends identifying the drug by finding the absorption peak in the ultraviolet part of the spectrum, which for an alcohol solution of the drug should correspond to a wavelength of 326 ± 1 nm.

The State Pharmacopoeia recommends determining the acid number for an oil solution of retinol acetate. This number characterizes not only the identity of the drug, but also the degree of its purity and should not exceed 1.0.

The quantitative determination is performed by spectrophotometry similar to the crystalline preparation.

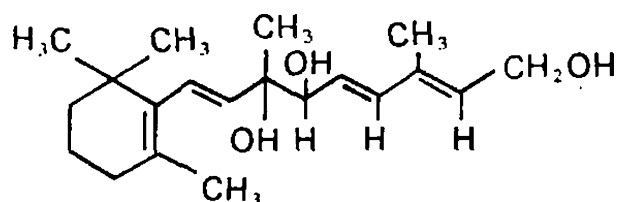
In 1937, vitamin A₂ was isolated from the livers of fresh-water fish. Its biological activity is 40% of that of vitamin A. These two substances have a close molecular mass and chemical properties.

The structural formula of vitamin A₂ differs from that of vitamin A in that the β-ionone ring has another double bond, hence it is called dehydroretinol:

Vitamin A₂

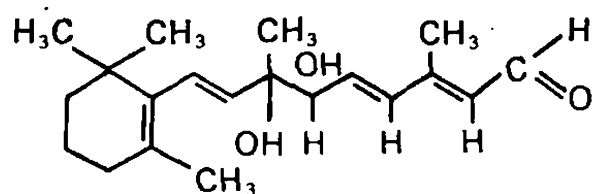
A substance similar in its properties and action to vitamin A, but having a different absorption spectrum, was discovered in whale livers. This substance was named vitamin A₃.

Retinol antivitamins. The hydroxylation of a double bond of a retinol or β-carotene carbon chain yields compounds with an antivitamin activity, i.e. retinol antivitamins:



Antivitamin A

The oxidation of retinol also yielded an antivitamin A having the following structure:



Antivitamin A

Vitamin A is very important for an organism. It is required for the growth and reproduction of cells and facilitates normal metabolism. It is also needed for normal functioning of the organ of vision. In avitaminosis A, the first to be affected is the organ of vision (night blindness); a prolonged deficiency of vitamin A may cause xeroma (xerophthalmia), a disease characterized by a dry shrunken appearance of the conjunctiva.

Vitamin A preparations include cod liver oil, dragée and oil solutions containing it, and also a synthetic vitamin A—axerophthol acetate.

Preparations of vitamin A should be stored in a place protected from light at a temperature up to 10 °C. It is listed in Group B.

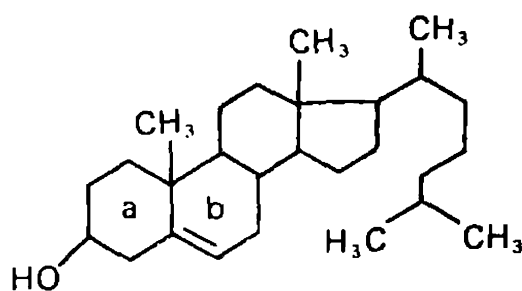
CALCIFEROLS (GROUP D VITAMINS)

Vitamin D is a specific vitamin required to prevent avitaminosis associated with rickets in children. This disease is due to the disturbance of salt metabolism, chiefly of calcium and phosphorus. The main importance of vitamin D is that it promotes the absorption of calcium and phosphorus from the bowel, which ensures the mineralization of the teeth and bone tissue of a growing organism.

Vitamin D is contained in large amounts, in addition to vitamin A, in the liver and fat tissues of fish, especially cod, and in the liver of the seal and other sea animals. It is contained in small amounts in the yolks of eggs, in caviar, butter, and milk.

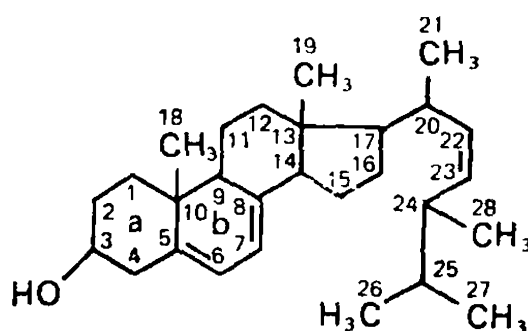
Observations revealed that vegetable oils such as linseed and cottonseed oils, and also some animal fats and oils (cod liver oil) after their irradiation by ultraviolet light acquire antiricket properties. Consequently, light stimulates the formation of an active substance preventing rickets, which was later called vitamin D. It was subsequently found that not the fats and oils themselves, but the sterols contained in them acquire an antiricket activity under the action of light. Sterols are an important constituent part of plant and animal organisms.

For example, cholesterol, contained in almost all the tissues of an animal organism, has the structure of a sterol:



Cholesterol

Sterols of a plant origin (phytosterols) such as ergosterol first isolated from the ergot and then from yeast, differ from cholesterol in having two additional double bonds in their molecule, one of which is in the side chain:

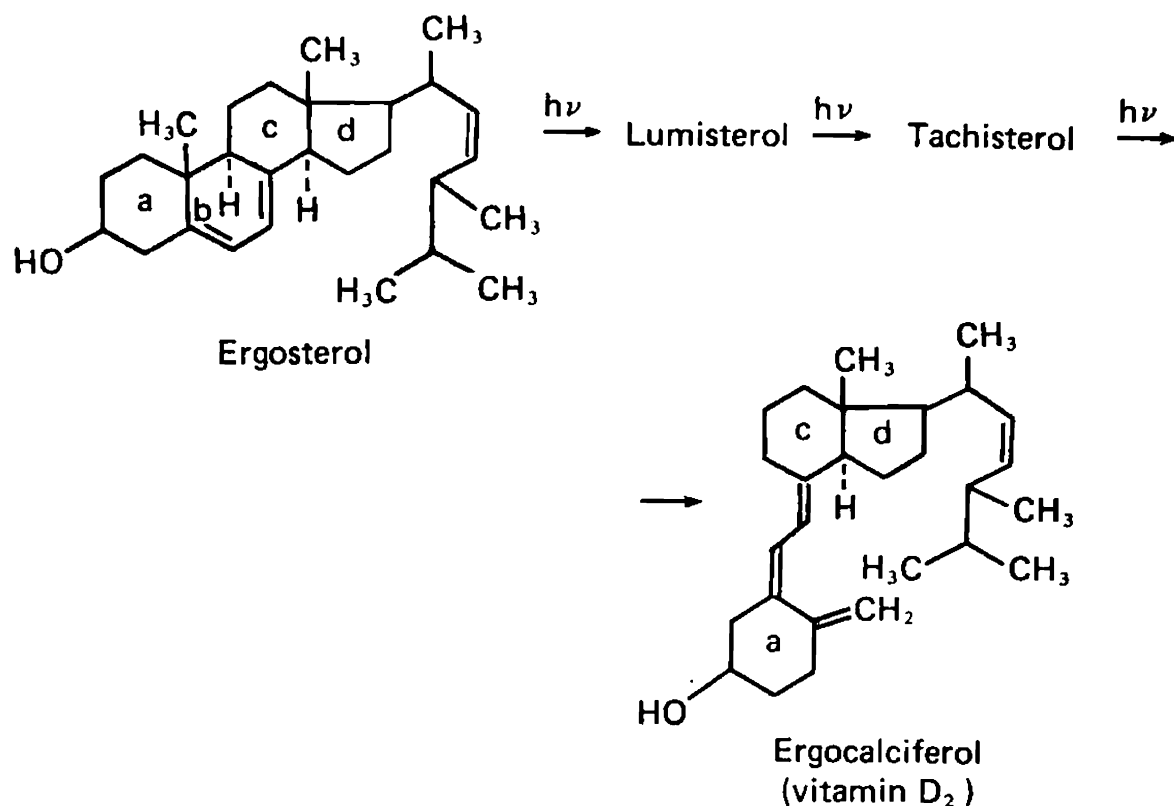


Ergosterol

Later ergosterol was produced from the residues of penicillin production and from a specially cultivated species of mould.

Investigations showed that not all sterols yield vitamin D when irradiated. If cholesterol is irradiated by ultraviolet light, the products do not reveal any activity against rickets, whereas the irradiation of ergosterol yields a highly active product—vitamin D₂. Consequently, ergosterol is the provitamin of D₂.

Vitamin D₂ is not obtained directly when ergosterol is irradiated, but via a number of intermediates:



The conversion of one substance into another in the irradiation of ergosterol depends on the wavelength. The maximum absorption of light is observed at 265 nm (in hexane or ether), which is characteristic of the formation of vitamin D₂. Further irradiation results in the formation of suprasterol and toxisterol, which no longer have the activity of vitamin D₂ and are very toxic. To prevent their formation, the process of photolysis must be controlled very thoroughly with no excessive radiation tolerated.

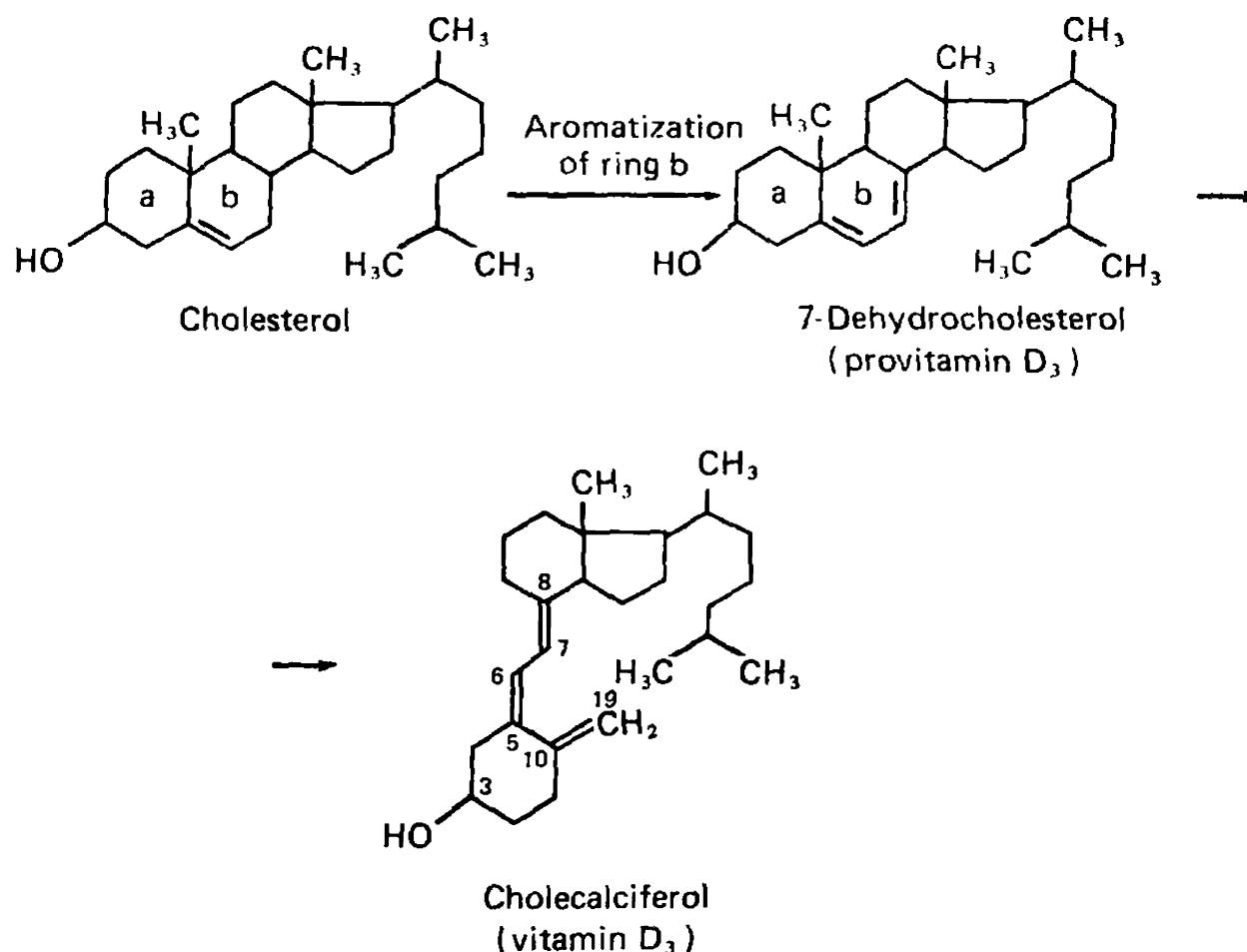
Of major significance in photolysis is the choice of the light source, solvents, and duration of irradiation. Generally an argon-mercury-quartz lamp is employed as the light source.

After the irradiation of ergosterol and purification of the photolysis products, two substances with a different degree of activity are obtained: (1) vitamin D₁—irradiated ergosterol with an admixture of lumisterol, and (2) vitamin D₂ (ergocalciferol)—irradiated ergosterol purified of all admixtures and having a high antirachitic activity.

Of major significance for the manifestation of antirachitic activity is the structure of ring b in the sterol molecule, which is opened between carbon atoms 9 and 10 with the formation of a third double bond (see the formula of vitamin D₂). The presence of a double bond in a side chain of a sterol molecule is not essential, but there must be three double bonds in a molecule.

Thus, only those sterols have an antirachitic effect when irradiated that have two double bonds in ring b.

It is thus clear why cholesterol does not yield a physiologically active product after direct irradiation (there is only one double bond in ring b of its molecule). To obtain a product with antirachitic activity from cholesterol, its molecule should be aromatized prior to irradiation, i.e. the lacking double bond should be introduced into ring b, and only then should it be irradiated. The product is cholecalciferol, called vitamin D₃:



The vitamins D₄, D₅, D₆, and others differing from vitamin D₃ only in the side chain in the sterol molecule are produced in a similar way when their provitamins (the relevant sterols) are irradiated.

Thus, the term "vitamin D" has a collective meaning that includes the entire group of compounds with a D-vitamin activity similar in their chemical structure.

Vitamin D₂ (ergocalciferol) in the pure form is composed of colourless prismatic or acicular crystals without an odour. Its melting

point is 120-121 °C. It is dextrorotatory. All the calciferols are soluble in all the conventional organic solvents and in fats, and are insoluble in water.

Crystalline vitamin D₂ is unstable and in two or three days begins to decompose at room temperature. When heated above 125 °C, it decomposes. But in oil solutions protected from the action of light, vitamin D₂ can retain its activity for several years.

In a neutral and alkaline medium, vitamin D₂ is stable thermally, while in an acidic medium it decomposes. The presence of small amounts of toxisterol and other irradiation products in solutions of vitamin D₂ lowers the stability of the vitamin.

Vitamin D₂ is identified by its reaction with an antimony(III) chloride solution. Here an orange-pink colour appears, while vitamin A produces a blue colour with this reagent.

Other colour reactions are also known, namely, with pyrogalllic acid, trichloroacetic acid, saccharose, aromatic aldehydes, etc. All these reactions can be used both for a qualitative and quantitative determination of the vitamin.

The pharmacopoeial preparation of vitamin D₂ is a 0.125% solution of ergocalciferol in oil (*Solutio Ergocalciferoli oleosa 0.125%*). It is a transparent oily liquid from a light yellow to a dark yellow colour.

The preparation is identified with an antimony(III) chloride solution and by thin-layer chromatography. It is recommended to determine the content of the preparation by photoelectrocolorimetry, employing the colour reaction with an antimony(III) chloride solution.

The main function of vitamin D is regulation of the phosphorus and calcium metabolism in an organism, promoting of the absorption of these substances by the bowel and their deposition in growing bones. Vitamin D is dispensed in the form of the following drugs:

- (1) vitaminol—an oil solution of ergosterol irradiated by ultraviolet light. It is dispensed in 10- and 35-ml bottles;
- (2) an alcohol solution of vitamin D dispensed in 35-ml bottles;
- (3) dragée of vitamin D; and
- (4) cod liver oil containing vitamin D together with vitamin A.

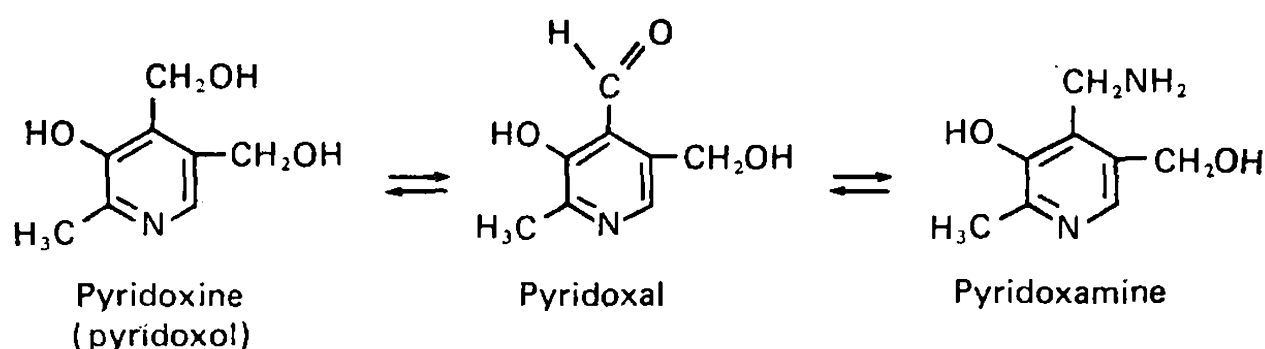
Vitamin D preparations including cod liver oil should be stored in dark glass bottles in the dark without the access of air because these factors deactivate vitamin D: the oxygen of the air oxidizes it, while light converts it into the very poisonous toxisterol.

30.3. HETEROCYCLIC DERIVATIVES

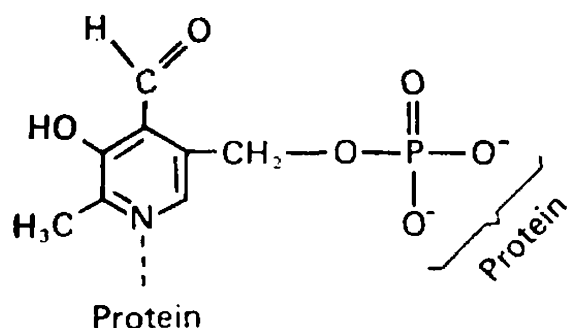
HYDROXYMETHYLPYRIDINE DERIVATIVES (GROUP B₆ VITAMINS)

Vitamins of this group contain the pyridine ring in their molecules. The main representative is vitamin B₆, which combines a group of three related compounds that are widespread in nature, namely, pyridoxine (pyridoxol), pyridoxamine, and pyridoxal.

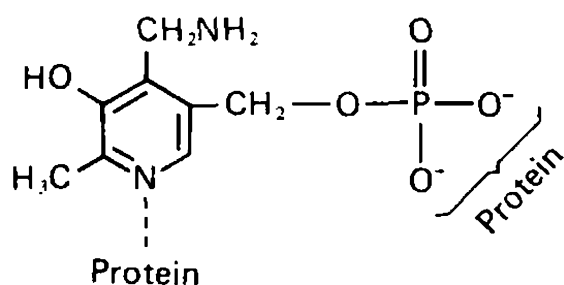
These substances are close in their chemical structure and can transform into one another:



The pyridoxine vitamins in an organism are converted into pyridoxal- and pyridoxamine-phosphate proteids, i.e. co-enzymes, that play the role of catalysts in nitrogen metabolic processes:



Pyridoxal-phosphate proteid



Pyridoxamine-phosphate proteid

Vitamin B₆ participates in various transformations of amino acids in an organism (reactions of transamination, decarboxylation, desulphuration, etc.). It has been established that the products of conversion of pyridoxol, i.e. pyridoxal and pyridoxamine, mainly act in an organism, hence pyridoxol is a provitamin of vitamin B₆.

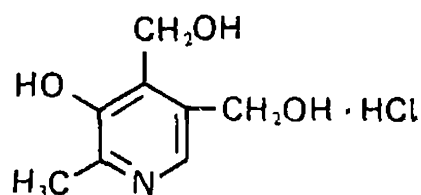
Vitamin B₆ was first obtained in the crystalline form from yeast in 1937 by Soviet researchers, and in 1938 from rice bran in the USA.

Vitamins of the B₆ group are thermally stable and stable in acids and alkalies, but are not stable to oxidizing agents. Light pro-

motes oxidation processes, which must be taken into consideration in their storage. The pharmacopoeial preparation of vitamin B₆ is pyridoxine hydrochloride.

Pyridoxine Hydrochloride (*Pyridoxini hydrochloridum*)

2-Methyl-3-hydroxy-4,5-di(hydroxymethyl)pyridine hydrochloride



$C_8H_{11}NO_3 \cdot HCl$

M.m. 205.64

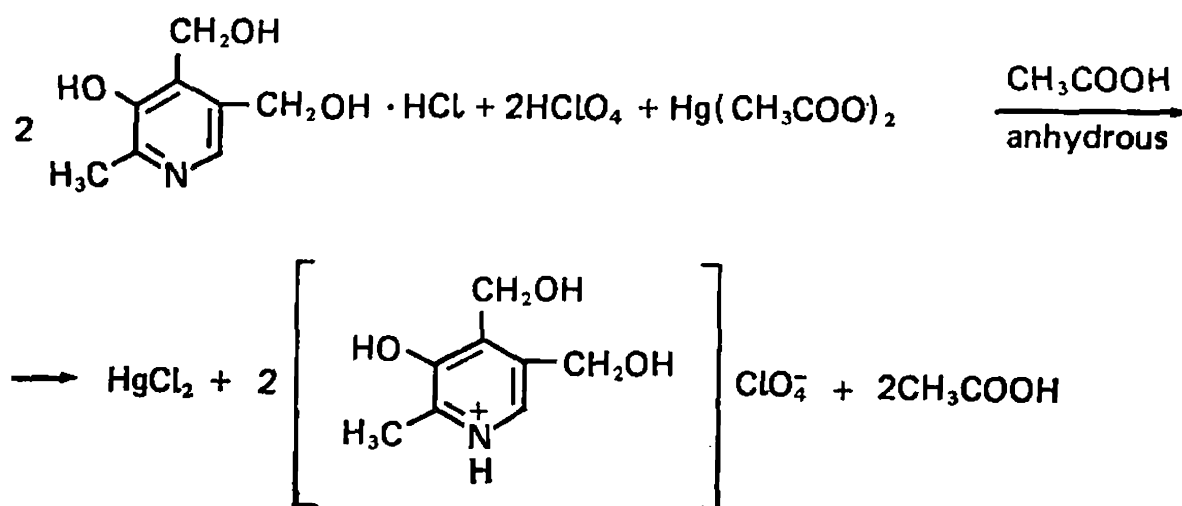
It is prepared synthetically. Pyridoxine hydrochloride is a white finely crystalline powder with a bitter and acidic taste. It dissolves readily in water, sparingly in alcohol, and is practically insoluble in ether. Its aqueous 1% solutions have a pH of 3.0 to 3.2.

The chemical properties of this vitamin are due, on the one hand, to the properties of the pyridine ring, and on the other to the properties of the substituents in the ring. Tertiary nitrogen in the molecule underlies the reactions of precipitation of pyridoxine hydrochloride by complex acids, i.e. by phosphotungstic and silicotungstic acids, Dragendorff's reagent, and other alkaloid reagents.

The phenol hydroxyl group is detected by a reaction with an iron(III) chloride solution (a red colour that vanishes when a few drops of dilute sulphuric acid are added) and by a coupling reaction with 2,6-dichloroquinonchlorimide (a blue indophenol dye forms). This reagent reacts only with phenols in which the *para*-position is not substituted. The latter two reactions are official ones.

Two methods are recommended by the State Pharmacopoeia for the quantitative analysis of pyridoxine hydrochloride:

(1) acid-base titration in non-aqueous media:



(2) neutralization with respect to the bound hydrochloric acid. A weighed sample of the drug is titrated with an alkali using a bromothymol blue indicator until a light blue colour appears:



Pyridoxine hydrochloride is used to treat toxicosis in pregnancy, pellagra (together with nicotinic acid), various kinds of parkinsonism, acute and chronic hepatitides, etc.

The drug is prescribed for oral, subcutaneous, intramuscular, intravenous administration.

It is dispensed in powders, tablets, or in ampoules containing 1 ml of a 1% or 5% solution.

It should be stored in well closed orange glass jars in a cool place, tablets and ampoules—in a place protected from light.

PYRIMIDINE-THIAZOLE DERIVATIVES (GROUP B₁ VITAMINS)

Vitamin B₁ (thiamine) is one of the first vitamins from which the science of vitaminology began. Its discovery was associated with interesting observations. At the beginning of the present century, the disease beriberi (Singhalese, reduplication of beri, weakness) became endemic in eastern and southern Asia, and among sailors. Its name is associated with diseases of the motor and sensory nerves.

Physicians explained the cause of this disease differently. Some considered it to be the result of infection, others found its origin in the use of polished rice.

This disease was produced in poultry given polished rice, and was called polyneuritis. It was found that polyneuritis in poultry and beriberi in humans is the same disease caused by the absence of a substance in polished rice. The Polish biochemist K. Funk later succeeded in isolating this substance first from rice bran, and then from yeast. It was originally named aneurin(e), and later, after its chemical formula was established, thiamine, because an amino group and sulphur were detected in its molecule.

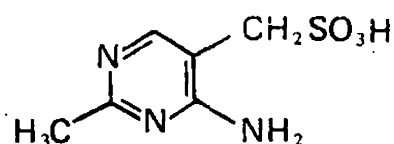
Vitamin B₁ (thiamine) is of major significance for an organism. It is a part of the coenzyme cocarboxylase that catalyzes the reactions of decarboxylation of pyrotartaric acid whose accumulation in the process of carbohydrate metabolism disturbs the normal functioning of the nervous system and causes polyneuritis. This is the main biological role of vitamin B₁.

In addition, thiamine diphosphate (a coenzyme) is contained in many other enzymes bound to a protein. Thiamine is also associated with the function of the haemopoietic organs, and participates in the metabolism of carbohydrates, fats, and mineral salts.

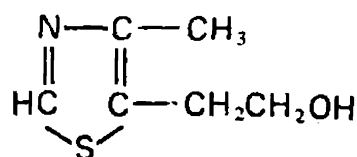
Vitamin B₁ is contained in large amounts in yeast and the germ and bran of cereals, and in rye and wheat bread.

Originally thiamine was produced from natural sources—rice bran and yeast, but the yield of pure thiamine was insignificant. For example, only 5 g of pure thiamine were obtained from a tonne of rice bran, and 0.25 g from a tonne of yeast. Such a low yield of the product could not satisfy the demand for this vitamin, and synthetic methods of producing it were put on the agenda.

The synthesis of thiamine was preceded by a great deal of work to establish the structure of natural thiamine. The latter was subjected to sulphite decomposition at a pH of 4.8-5 and at room temperature. Two substances were obtained, namely, pyrimidineamino-sulphonic acid (I) and 4-methyl-5-hydroxyethylthiazole (II):

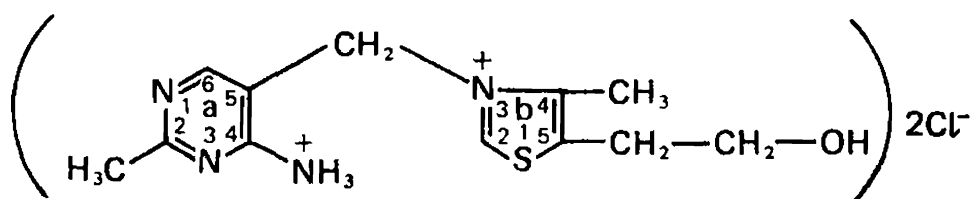


I



II

Studying of the decomposition products of the natural vitamin B₁ revealed that its formula consists of two heterocycles—a pyrimidine one (a) and a thiazole one (b) bound together by a methylene group:



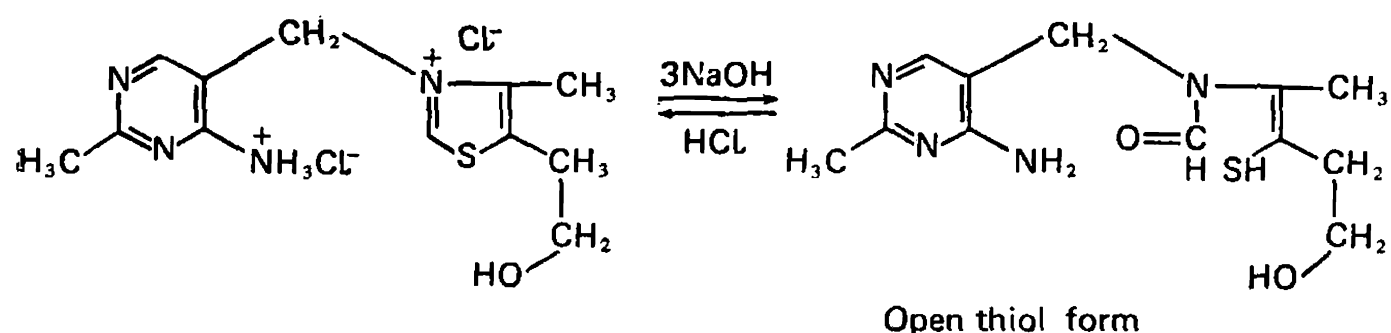
The structure of the thiamine molecule was finally established by R. Williams and was later confirmed by synthesis.

Inspection of the formula of thiamine reveals that the pyrimidine ring contains an amino group (NH₂) in position 4; it imparts basic properties to the compound and, consequently, an ability to form salts with acids.

The thiazole ring contains a methyl group in position 4 and a hydroxyethyl group in position 5 that can produce esters with acids. The nitrogen in position 3 of the thiazole ring underlies the formation of quaternary ammonium salts (in the given case, the chloride of the quaternary ammonium salt). Hence, the chemical name of thiamine is 3-(4-amino-2-methyl-5-pyrimidylmethyl)-5-(2-hydroxyethyl)-

4-methylthiazolium chloride hydrochloride. This formula was confirmed by the synthesis of thiamine.

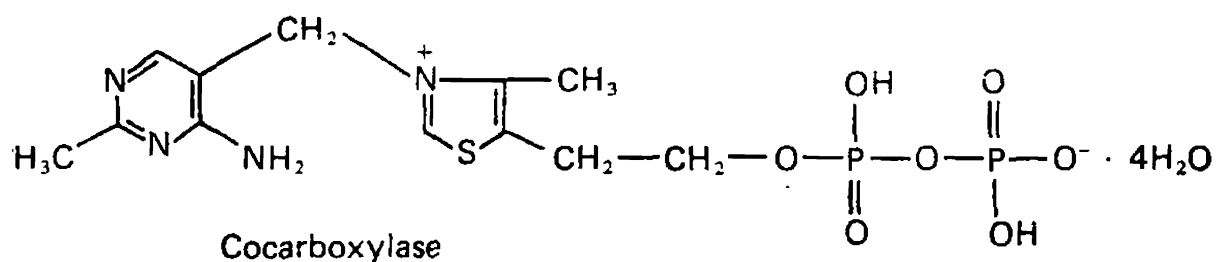
The chemical properties of thiamine are chiefly determined by the thiazolium ring, which under the influence of an alkali (NaOH) decomposes and transforms into the open thiol form. The action of an acid (HCl) causes the latter to form thiamine again:



The thiol form retains the physiological activity of vitamin B₁, and a variety of modified derivatives of the thiol form of vitamin B₁ were produced and studied (especially disulphide thiamine derivatives). These compounds attracted attention because the enzyme thiaminase, produced by the normal intestinal microflora and contained in considerable amounts in fish products, decomposes vitamin B₁ in an organism, but does not decompose the thiol derivatives of thiamine. Since the latter are physiologically active, the vitamin can be retained in the amount needed by an organism.

Of the other thiamine derivatives, of interest for medicine are the ethers of thiamine with phosphoric acids formed owing to the hydroxyethyl group of thiamine (a primary alcohol group).

The thiamine taken in with food is absorbed from the intestines via the blood into the tissues, where it is subjected to phosphorization. The formed thiamine diphosphate (TDP) or cocarboxylase is a biological catalyst participating in the decarboxylation of pyrotartaric acid. The latter, being a product of carbohydrate metabolism, has a toxic action on the nerve cells, causing polyneuritis:

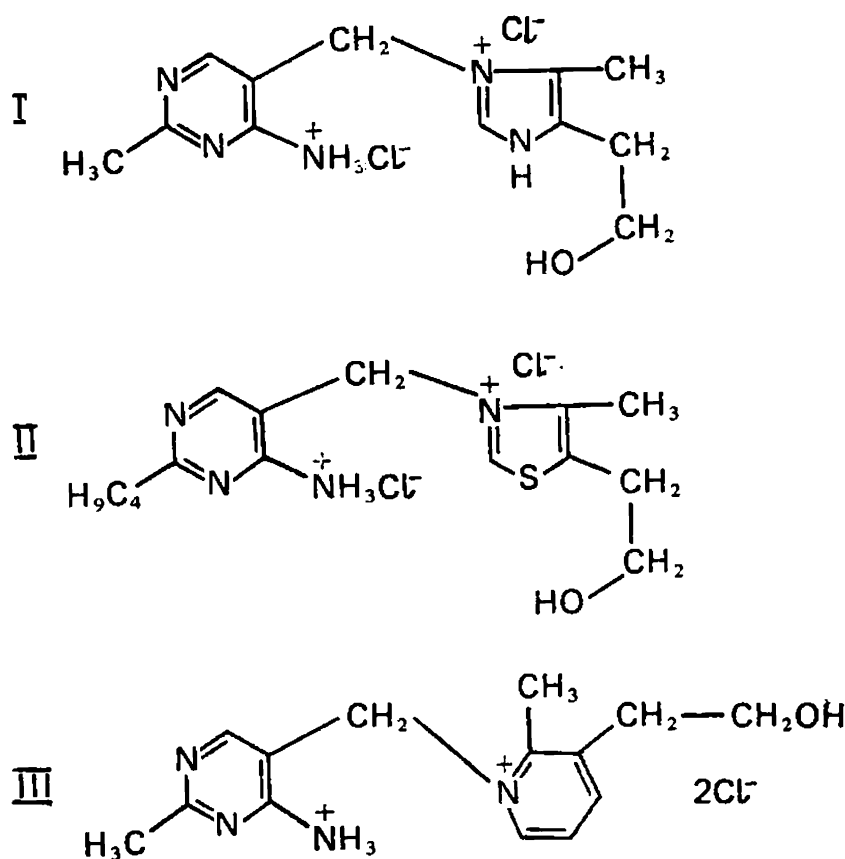


Cocarboxylase has been produced synthetically and its hydrochloride is a medicinal preparation.

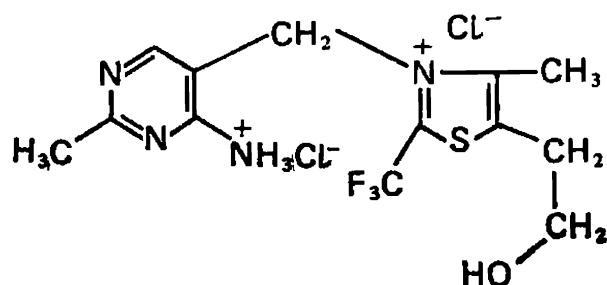
For thiamine to exhibit a physiological action, its molecule must be specific. A change in the structure of the molecule and separate functional groups results in a sharp change in the physiological action of the vitamin. For example, if the amino group in position 4

of the pyrimidine ring is replaced with a hydroxyl group, the physiological activity disappears. Replacement of the methyl group in position 4 of the thiazole ring with an ethyl one halves the activity of the vitamin, while when this group is simultaneously introduced in position 2 of the pyrimidine ring, it is reduced six times. All other changes in the thiamine molecule, for example, transition of the amino group to position 4 and the introduction of substituents into the pyrimidine ring lower its activity scores and hundreds of times, while sometimes a complete loss of the biological activity occurs.

The thiazole ring also affects the physiological activity of vitamin B₁. In a number of cases, its replacement with other heterocyclic systems yields compounds paralyzing the action of vitamin B₁. For example, the imidazole analogue (I) and 2-*n*-butylpyrimidine analogue (II) are antagonists (antivitamins) of vitamin B₁. The pyridine analogue (III) is a still stronger antagonist:



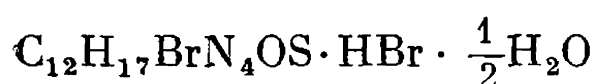
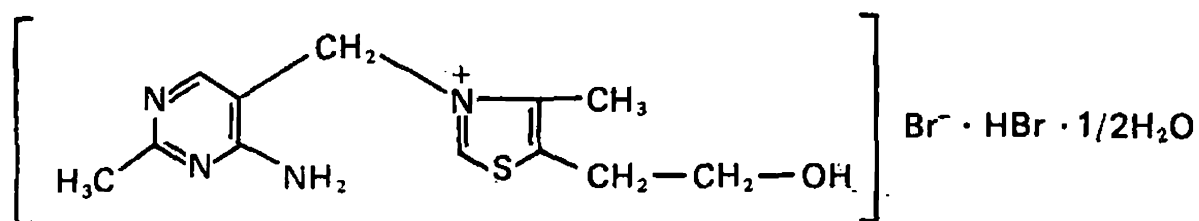
In recent years, another synthetic antagonist of vitamin B₁ has been discovered, namely, 2-trifluoromethylthiamine:



It has been established that this inhibitor suppresses the development of leukaemia. The pharmacopoeial preparations of thiamine are thiamine bromide and thiamine chloride.

Thiamine Bromide (*Thiamini bromidum*)

3-(4-amino-2-methyl-5-pyrimidylmethyl)-5-(2-hydroxyethyl)-4-methylthiazolium bromide hydrobromide

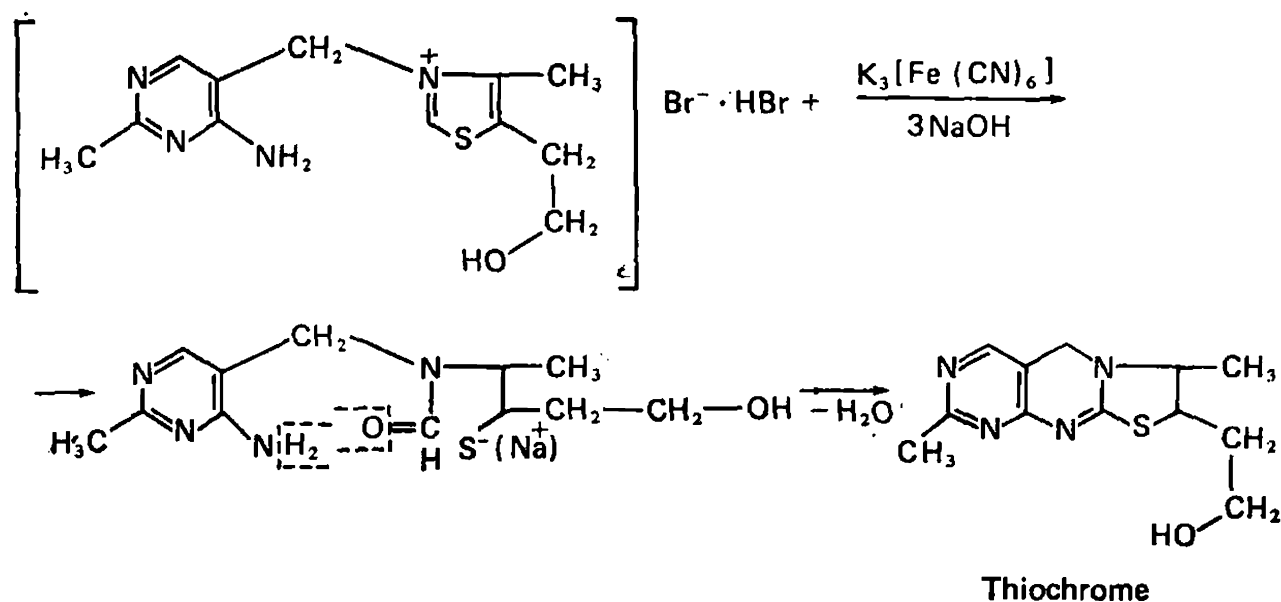


M.m. 435.2

Thiamine bromide is a white powder, sometimes with a slightly yellowish tint, having a weak specific odour. It dissolves readily in water and methanol, with difficulty in ethanol, and is insoluble in ether.

In a strongly acidic medium, thiamine bromide is stable and does not decompose even under the action of oxidizing agents such as hydrogen peroxide, potassium permanganate, and ozone. At a pH of 3.5, thiamine can be heated to 120 °C without any decomposition. Vitamin B₁ does not decompose or become oxidized under the action of light and oxygen, but decomposes rapidly in an alkaline medium with the formation of the open thiol form.

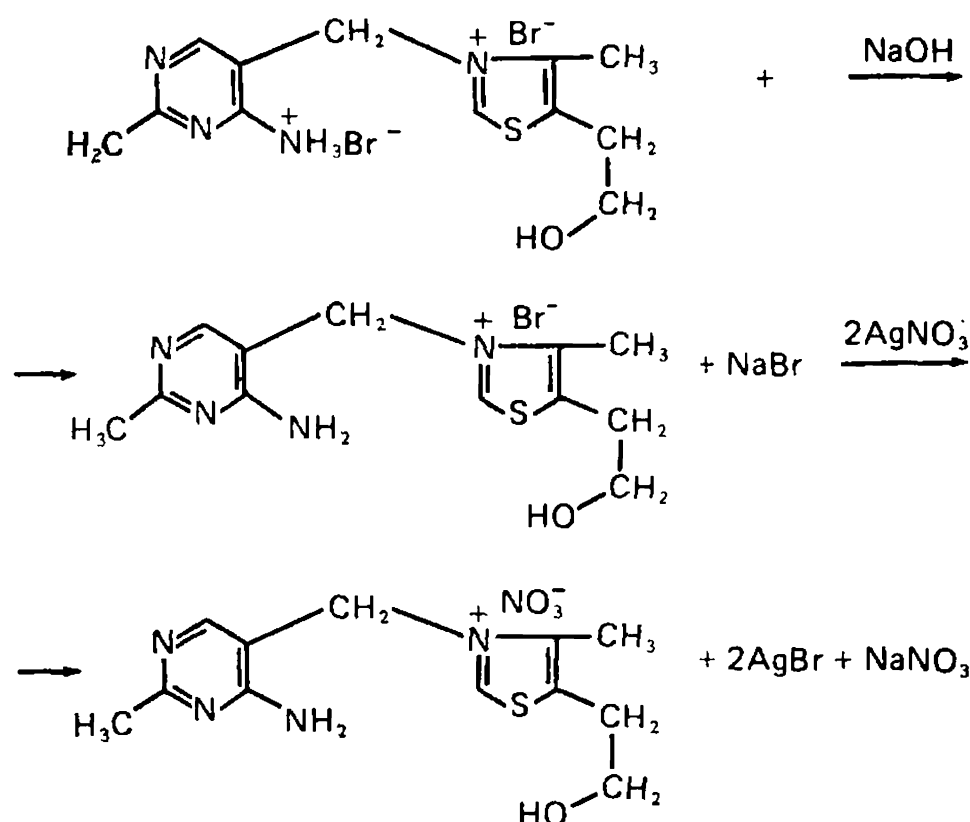
The oxidation of the thiol form of thiamine is used to identify the drug. The State Pharmacopoeia recommends the reaction of formation of a thiochrome. When thiamine hydrobromide is reacted in an alkaline medium with a potassium ferricyanide solution, a yellow thiochrome forms, while in ultraviolet light an intensively blue fluorescence appears that vanishes with acidification and again appears when the solution is alkalized:



The drug gives the characteristic reactions for bromides.

The State Pharmacopoeia recommends determining the content of thiamine bromide by the gravimetric method. For this purpose, a hot solution of the drug acidified with hydrochloric acid is treated with silicotungstic acid $12\text{WO}_3 \cdot \text{SiO}_2 \cdot 12\text{H}_2\text{O}$. The formed precipitate of a complex salt is filtered through a preliminarily weighed glass filter, and is rinsed with hot dilute hydrochloric acid and acetone. The filter with the precipitate is dried over phosphorus(V) oxide at $100-105^\circ\text{C}$ up to a constant mass. The mass of the precipitate multiplied by 0.25 corresponds to the amount of thiamine bromide whose content in the drug should be at least 98%.

The content of the drug can also be established by argentometry after its neutralization with an alkali (NaOH) using bromothymol blue as the indicator:



The difference between the number of millilitres of the silver nitrate solution and that of the sodium hydroxide solution is converted to thiamine bromide (the official method).

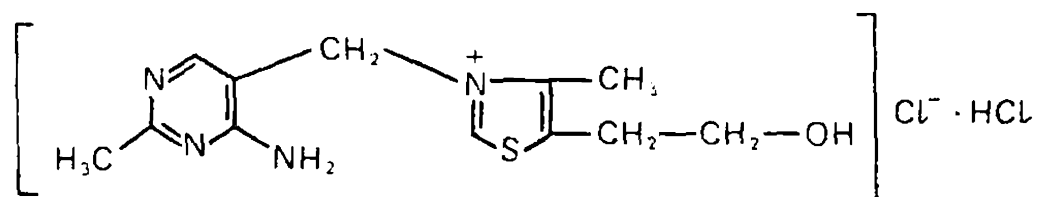
The vitamin B₁ drugs thiamine bromide and thiamine chloride are taken orally and parenterally in B₁ avitaminosis, neuritis, neuralgia, and peripheral paralysis.

Thiamine bromide is dispensed in powders, dragée, tablets, and ampoules containing 1 ml of 3% or 6% solutions.

It should be stored in sealed containers protecting it from the action of light.

Thiamine Chloride (*Thiaini chloridum*)

3-(4-amino-2-methyl-5-pyrimidylmethyl)-5-(2-hydroxyethyl)-
4-methylthiazolium chloride hydrochloride



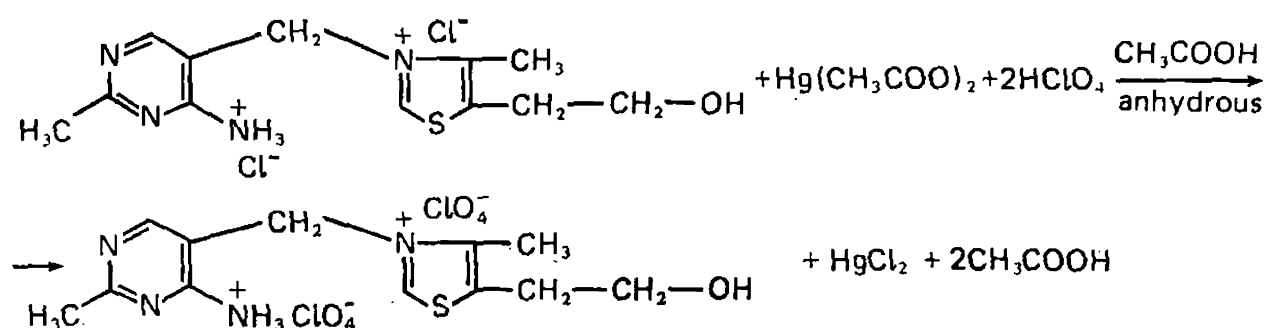
$\text{C}_{12}\text{H}_{17}\text{ClN}_4\text{OS} \cdot \text{HCl}$

M.m. 337.27

Thiamine chloride is a white crystalline hygroscopic powder with a weak characteristic odour. It dissolves readily in water, sparingly in ethanol, and is insoluble in ether, acetone, benzene, and chloroform.

Its chemical properties and methods of analysis are similar to those of thiamine bromide.

The content of thiamine chloride is determined by acid-base titration in non-aqueous media (the official method):



For the quantitative analysis of thiamine chloride in tablets, the State Pharmacopoeia recommends the fluorimetric method with a reaction of thiochrome formation.

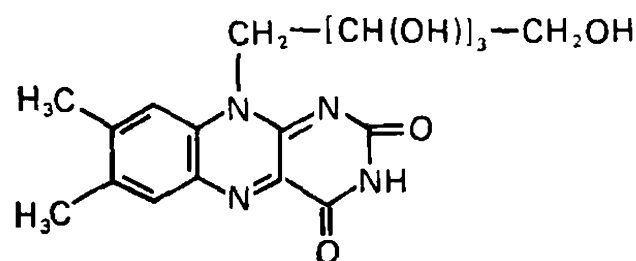
It is dispensed in powders, tablets, dragée, and ampoules containing 1 ml of 2.5% and 5% solutions.

The storage conditions are the same as for thiamine bromide.

30.4. ISOALLOXAZINE DERIVATIVES (GROUP B₂ VITAMINS)

Riboflavine (*Riboflavinum*)

6,7-Dimethyl-9-(D-1-ribityl)-isoalloxazine

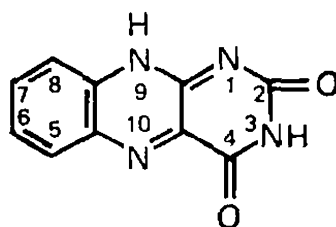


C₁₇H₂₀N₄O₆

M.m. 376.37

Vitamin B₂ was first isolated from milk whey in the form of a yellow pigment called lactochrome. Next "Warburg's yellow enzyme" consisting of a protein and a yellow dye was isolated from yeast. The dye was identified as vitamin B₂ and was called lactoflavine. Similar yellow pigments (flavins) were isolated from egg yolks (ovoflavin), lemons (citroflavin), the liver (lyochrome), and so on.

All these flavins in the pure form had an identical B₂-vitamin activity and in their chemical structure was found to be the same, all of them containing the isoalloxazine nucleus:



Examination of the formula reveals that the isoalloxazine nucleus is a condensed system of three rings, namely, pyrimidine (1,2,3,4), pyrazine (9,10), and benzene (5,6,7,8). After the lactoflavine molecule was found to contain the sugar ribose, the name "lactoflavine" was changed to "riboflavine". The latter name of vitamin B₂ is still in use at present.

Riboflavine is a group name combining all the flavins with B₂-vitamin activity and similar in structure to vitamin B₂. Riboflavine is encountered in the free form only in milk, urine, and in the retina of the eye. In all other natural sources (yeast, liver, wheat, barley, spinach, tomatoes), it is in the form of mono- or dinucleotides (co-enzymes). It is contained in the form of a co-enzyme in a number of enzyme systems regulating the oxidation processes in cells.

Riboflavine participates in the synthesis of proteins and fats, influences the state of the central nervous system, and the metabolism processes in the cornea and retina of the eye, i.e. the function of

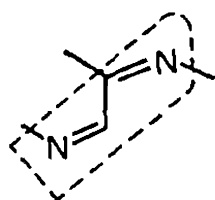
vision. Insufficient vitamin B₂ in an organism first of all affects the mucous membrane of the mouth and eyes.

The structure of riboflavin was established by studying the products of its decomposition and complete synthesis. The latter was carried out in 1935 by P. Karrer and his co-workers.

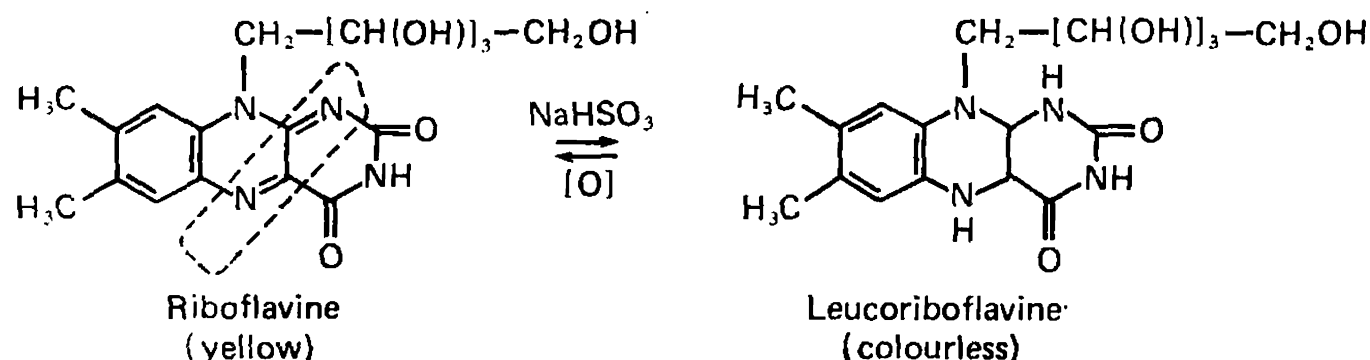
Since the recovery of riboflavin from natural sources is an involved process with a very low product yield, at present the vitamin is produced only synthetically.

Riboflavin is a yellow-orange crystalline powder. The crystals have the form of needles or druses. Riboflavin has a weak specific odour and a bitter taste. It dissolves only slightly in water, is insoluble in alcohol, ether, acetone, benzene, and chloroform. It dissolves in alkali solutions.

Neutral aqueous solutions of riboflavin have a bright greenish yellow colour due to the presence in the molecule of a chromophor (azomethine) group:



When illuminated by ultraviolet light, riboflavin solutions produce an intensive green fluorescence due to the presence of a free imine group in position 3 of the isoalloxazine nucleus. When an alkali or acid solution is added to a fluorescing solution, the fluorescence vanishes. When sodium hydrogen sulphite is added, the colour also vanishes because of the reduction of the riboflavin to the colourless compound leucoriboflavin, which when oxidized again transforms into riboflavin:



This reaction is employed to identify the drug.

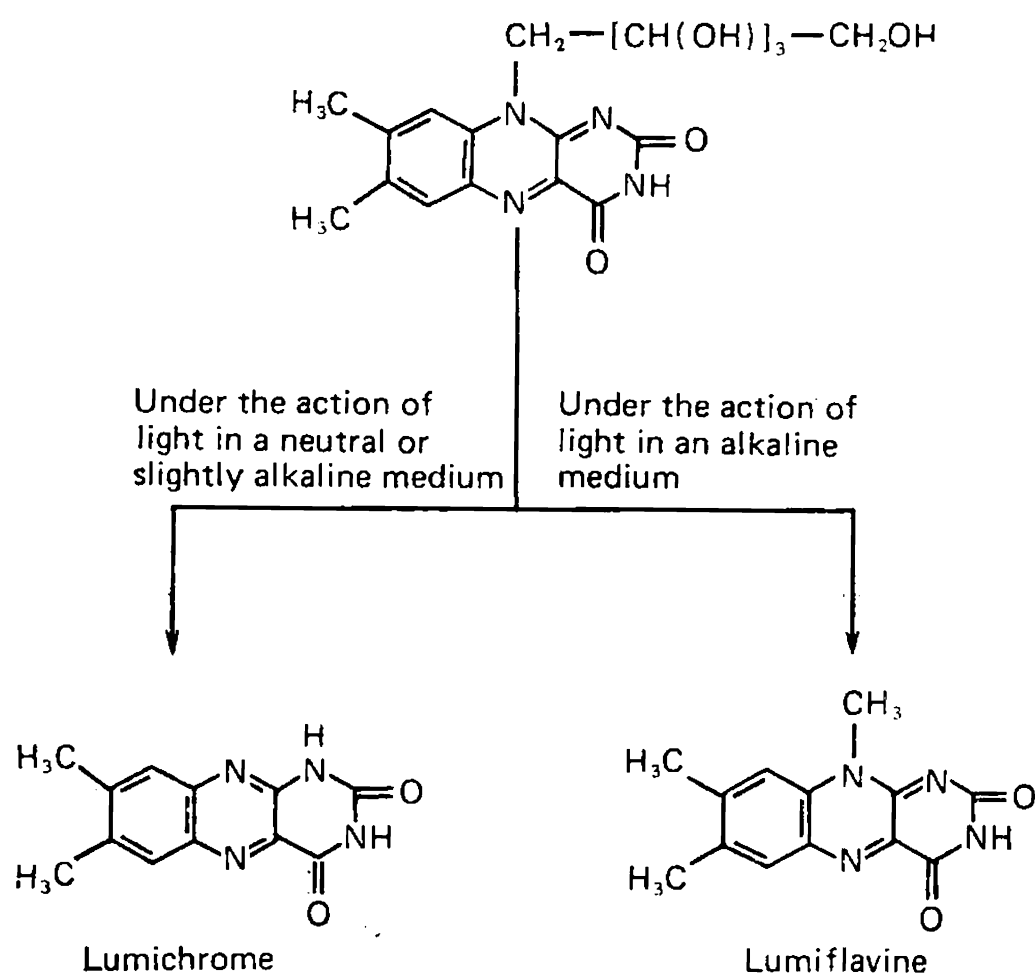
The ability of riboflavin to participate in oxidation-reduction reactions, due to the labile azomethine group (singled out by dashed lines) also underlies the biological activity of riboflavin.

Riboflavin can form esters with acids via the primary alcohol group of the sugar ribose. The ester of riboflavin with concentrated

sulphuric acid is coloured crimson and can be used to identify the drug.

Riboflavine forms complexes insoluble in water with salts of the heavy metals (Fe, Co, Ni, Zn, Cu, Ag). Some of them are coloured and can also be used for the identification of riboflavine. For example, riboflavine forms an orange-red complex with a silver nitrate solution in a neutral medium. This reaction can be used to identify riboflavine if there are no substances that can be oxidized by the silver nitrate (such as ascorbic acid) or react with it (such as halides).

Riboflavine is stable to oxidizing agents and heating. This distinguishes it from the other vitamins of group B. When heated in alkaline solutions, however, riboflavine rapidly decomposes. Its stability under the action of light is still greater. In light, it is unstable in both an acidic and an alkaline media. For example, when riboflavine is illuminated in an alkaline medium, lumiflavine forms, while in a neutral or weakly acidic medium lumichrome forms. In either case, the physiological activity of riboflavine disappears:



Lumiflavine and lumichrome can be undesirable admixtures in riboflavine when the drug is stored improperly.

Riboflavine is optically active (this is due to the presence in the ribityl chain of three asymmetric carbon atoms). It is levorotatory in weakly alkaline solutions, and has no optical activity in acidic and

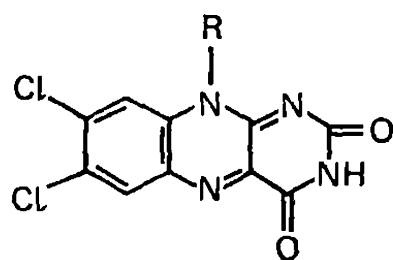
neutral solutions. This is why the State Pharmacopoeia recommends determining the specific rotation of its alkaline solution (of a definite concentration), which should range from -110° to -130° , to identify and check the purity of the drug.

Biological and physicochemical methods, namely, fluorometry, colorimetry, and spectrophotometry, are mainly employed for the quantitative analysis of riboflavine at present. The first of them is based on the ability of aqueous riboflavine solutions to produce an intensive yellow-green fluorescence. The colorimetric methods use colour reactions, i.e. Denigés's reagent (a solution of mercury(II) sulphate) as a result of which an orange colour appears; with a silver nitrate solution at a pH of 6.5-7.2, a red or pink-red colour appears (depending on the riboflavine concentration).

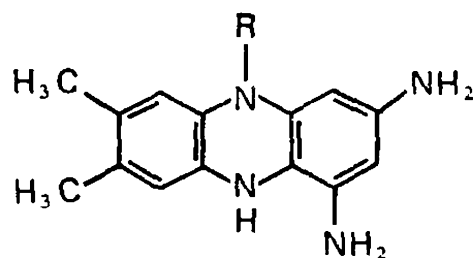
The State Pharmacopoeia recommends determining the amount of riboflavine by spectrometry because it can absorb radiant energy at a definite wavelength.

To exhibit vitamin B₂ activity, the riboflavine molecule must be specific. Even negligible changes in the structure of the molecule involve a decrease or complete vanishing of its activity. For example, the removal of the methyl groups from positions 6 and 7 or their transfer to positions 5 and 8 destroys the biological activity.

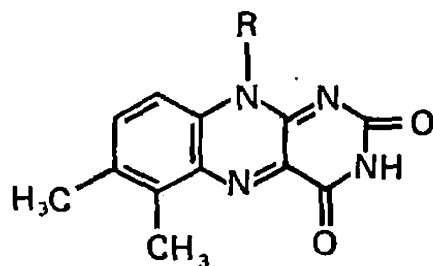
The main antagonists (antivitamins) of vitamin B₂ are:



6,7-Dichloro-9-ribityl-
isoalloxazine



2,4-Diamino-6,7-dimethyl-9-ribityl
dihydrophenazine



Isoriboflavine

where R is ribose.

Of substantial importance for the exhibition of vitamin B₂ activity is also the presence of a free imino group in position 3 of the pyrimidine ring. The methylation of this imino group destroys the vitamin properties. This is apparently associated with the ability of the phosphoric ether of riboflavine to form an enzyme with a protein only via the imino group.

The presence of an imino group in the riboflavine molecule is also important because the physiological activity of the latter depends directly on the fluorescence produced by this group. An important role is also played by the nature of the carbon chain in position 9 of the molecule.

The replacement of the ribityl residue by another carbohydrate chain destroys the activity of the compound. A saccharose of the type of methylpentose is required to retain the vitamin activity.

The basic indications of B₂ deficiency in humans are diseases of the mucous membrane in the mouth cavity and lips, lesions at the angles of the mouth and on the lips, and inflammation of the skin near the ears and eyes. One of the specific symptoms of vitamin B₂ deficiency is a disease of the eyes (itch, burning, lacrimation, blurred vision) that transforms into inflammation of the eyeball with the development of a cataract. Vitamin B₂ deficiency often causes anaemia and dermatitis. This explains the wide use of riboflavine to treat diseases such as stomatitis, dermatitis, conjunctivitis, and cataracts.

Riboflavine is prescribed for oral taking in powders, tablets, dragée, and in eye drops (a 0.01% solution), and is dispensed in these forms.

With a view to its decomposition in the light, riboflavine should be stored in well closed orange glass jars, and tablets in a place protected from light.

30.5. COBALAMINS (GROUP B₁₂ VITAMINS)

Vitamin B₁₂ was discovered in 1948, when a dark red crystalline substance having a high activity against malignant (pernicious) anaemia was isolated from liver extract. The substance was called vitamin B₁₂. Its empirical formula shows that it contains cobalt, which determined its name cobalamin.

Vitamin B₁₂ is encountered widely in products of an animal origin, especially in the internal organs of fish, whale liver, and the meat of mollusks. It is also contained in poultry manure, the putrefied sludge of sewage refuse, and in the stomach contents of ruminant animals.

Further studies revealed that vitamin B₁₂, unlike all the other vitamins, is synthesized by microorganisms, including bacteria, moulds, and actinomycetes. In a human and animal organism, vitamin B₁₂ is synthesized by the microflora of the intestines, whence it is supplied and accumulated in the liver, kidneys, and intestine walls.

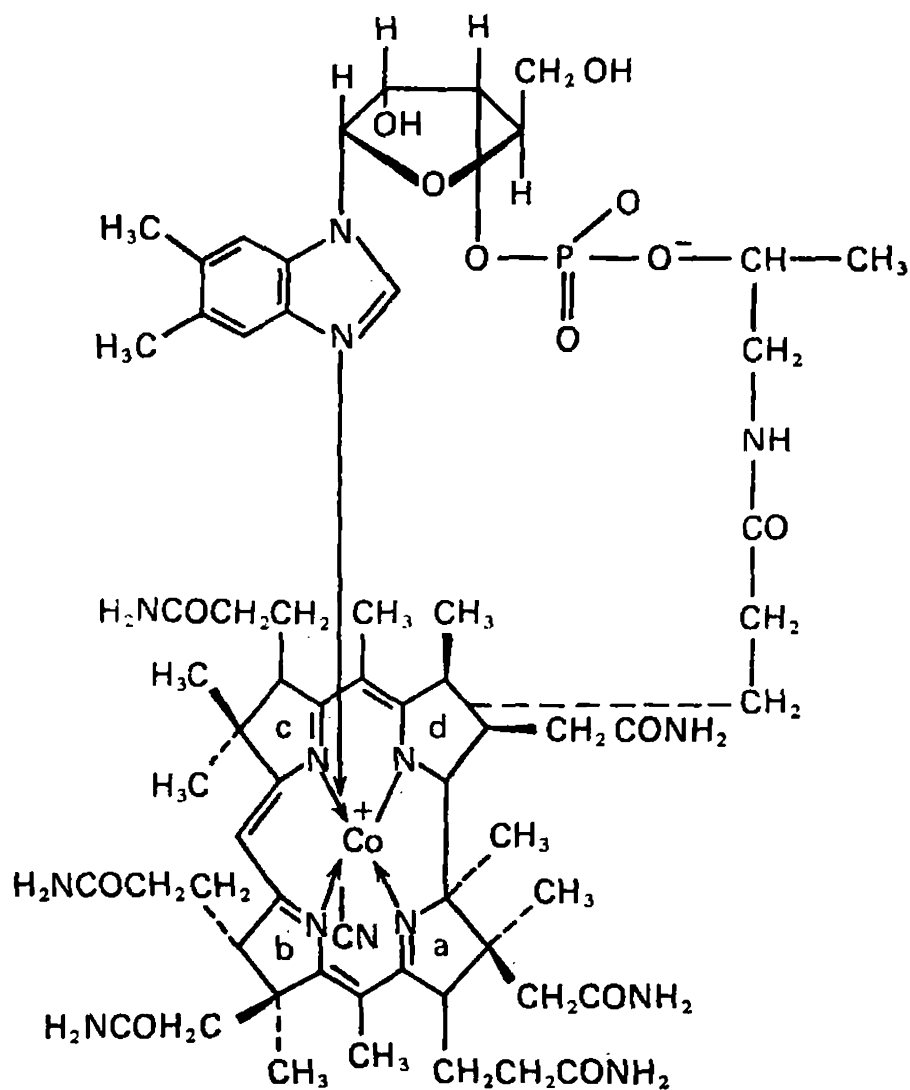
Prior to the discovery of vitamin B₁₂, no cases were known of the synthesis of vitamins by microorganisms. When it was established that vitamin B₁₂ is synthesized in the human organism by microflora in the intestines, nutrient media were developed for the arti-

ficial biosynthesis of vitamin B₁₂ by microorganisms. The addition of cobalt salts to them stimulates the biosynthesis of the entire vitamin. The most active strains of actinomycetes and bacteria were *Streptomyces griseus* (producing the antibiotic streptomycin), *Bacillus megatherium*, and the bacteria of propionic acid fermentation. They are what has been begun to be used for the commercial production of vitamin B₁₂.

In the Soviet Union, the production of vitamin B₁₂ is combined with the production of the antibiotic streptomycin, since they are synthesized from the same actinomycete (*Streptomyces griseus*). By changing the technological conditions, one can carry out the biosynthesis to obtain either vitamin B₁₂ (the addition of cobalt salts to the nutrient medium), or streptomycin.

The molecule of vitamin B₁₂ has a very complicated structure. Its central part has a porphyrin-like structure containing a cobalt atom and a cyano group forming a coordination complex, the cobalt having a coordination number of six. The cyano group bound to the cobalt determines the name of vitamin B₁₂—cyanocobalamin.

Cyanocobalamin (*Cyanocobalaminum*)



M.m. 1355.40

The vitamin B₁₂ molecule consists of two parts:

(1) a nucleotide, that is 5,6-dimethylbenzimidazole bound to the monosaccharide ribose, which is joined by an ether bond to phosphoric acid;

(2) a cobamide—the central part of the molecule, which is an amide of the hexabasic cobaminic acid containing cobalt. Cobaminic acid is based on a porphyrin system similar in its structure to blood haemin and chlorophyll. The only difference is that the inorganic element in haemin is Fe²⁺, in chlorophyll is Mg²⁺, and they have pyrrole rings. In the vitamin B₁₂ molecule, on the other hand, Co²⁺ is present, and the pyrrole rings are reduced to pyrroline and pyrrolidine ones.

In the vitamin B₁₂ molecule, the carboxyl groups of the hexabasic cobaminic acid are present in the form of amides, which is why the cobalt-containing part of the molecules is called cobamide. The cobamide part of the molecule has three free acetamide and three free propionamide groups. The fourth propionamide group binds the cobamide part of the molecule to the nucleotide via a propiol residue.

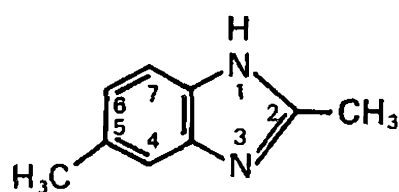
Thus, in the chemical respect, vitamin B₁₂ can be considered as a diether of phosphoric acid (one ether bond joins the phosphoric acid to the ribose, and the other to the propiol residue of the cobamide), in which the free negative charge of the phosphoric acid is neutralized by one positive charge of the cobalt. This is why the vitamin B₁₂ molecule can be considered as an inner salt.

The structure of the vitamin B₁₂ molecule was elucidated by D. Hodgkin (USA) in 1955 using X-ray crystallography (she was awarded the Nobel prize for this work in 1964). The complicated structure of the molecule was confirmed by complete chemical synthesis carried out in 1972 by the well-known organic chemist R. Woodward (USA).

Research has shown that under specific conditions, various analogues of vitamin B₁₂ can be obtained because the CN group in its molecule can be replaced by other groups of atoms. For example, the mild hydrolysis of vitamin B₁₂ yielded vitamin B_{12a} containing a hydroxy group instead of the CN one; for this reason it was called hydroxocobalamin. Under other conditions, nitritocobalamin containing a nitroso group (NO) instead of the CN group was prepared. Also known are sulphito-, iodo-, chlorocobalamins, and so on. When reacted with cyanide, these analogues again transform into cyanocobalamin. In this connection, all these analogues exhibit the physiological activity of vitamin B₁₂ to a various degree.

Other derivatives of vitamin B₁₂ were also obtained by changing the structure of the nucleotide part of the molecule. It was exactly the existence of a large number of vitamin B₁₂ analogues having a smaller or larger degree of biological activity that determined the group name of cobalamins.

Antagonists of vitamin B₁₂ were discovered comparatively recently, during the last decade. One of the most potent antivitamins of vitamin B₁₂ is the structural analogue of the nucleotide part of its molecule, namely, 2,5-dimethylbenzimidazole. It differs from the vitamin in that the methyl group of the benzene ring has been transferred to position 2 of the nucleotide molecule from position 6:



2,5-Dimethylbenzimidazole

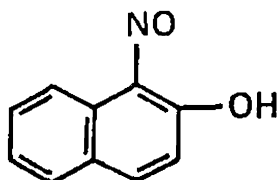
The pharmacopoeial preparation of vitamin B₁₂, cyanocobalamin, is a dark red crystalline powder having neither an odour nor a taste. It dissolves sparingly in water, is soluble in alcohol, and is insoluble in benzene, chloroform, ether, and acetone. The vitamin B₁₂ powder is hygroscopic, which must be taken into consideration when storing the drug.

Aqueous solutions of cyanocobalamin have a neutral reaction, and their colour ranges from bright red to pale pink depending on the concentration.

Vitamin B₁₂ crystals do not have a specific melting point. At 300–320 °C, they begin to melt with decomposition and become darker. When burnt, cobalt is detected in the residue. Its content in the vitamin is 4.5%.

The spectral characteristic of vitamin B₁₂ is mainly used to identify and establish its purity. Vitamin B₁₂ solutions have a characteristic absorption spectrum, namely, two peaks in the ultra-violet region of the spectrum at wavelengths of 278 and 361 nm, and one peak in the visible region of the spectrum at a wavelength of 548 nm. The absorptivities (extinction coefficients) a at these points are 115, 27, and 64, respectively. This spectral characteristic distinguishes vitamin B₁₂ from its derivatives, which in the majority of cases do not produce a characteristic absorption at the given wavelengths.

Colour reactions can also be used to identify cyanocobalamin. For example, the State Pharmacopoeia recommends the reaction with a solution of a nitroso-P-salt C₁₀H₄(NO)(OH)(SO₃Na)₂ after decomposition of the cyanocobalamin and the creation of a definite pH of the medium. The nitroso-P-salt can be replaced with 1-nitroso-2-naphthol:



Both reagents form a red complex with cobalt after decomposition of the vitamin molecule.

These colour reactions can also be employed for the quantitative analysis of the vitamin by photolorimetry. Photometric methods based on the natural colour of vitamin B₁₂ solutions are often used for a quantitative estimate of the vitamin. Spectrophotometry is the official method for the quantitative analysis of cyanocobalamin.

Vitamin B₁₂ is absorbed poorly when taken orally, therefore it is administered intramuscularly, subcutaneously, and intravenously. In addition to the crystalline drug, the State Pharmacopoeia lists a cyanocobalamin solution for injections (*Solutio Cyanocobalaminis pro injectionibus*).

Vitamin B₁₂ solutions are prepared with an isotonic sodium chloride solution.

Vitamin B₁₂ is effective against anaemia. It is needed for normal haemopoiesis and maturation of the erythrocytes. It participates in the synthesis of labile groups, and in the formation of choline, methionine, and nucleic acids. It is widely used to treat malignant anaemia.

It is dispensed in ampoules containing 30, 100, 200, or 500 µg of cyanocobalamin in 1 ml of an isotonic sodium chloride solution.

The crystalline drug should be stored in well closed jars in a place protected from light because vitamin B₁₂ absorbs up to 12% of moisture when stored with the access of air. Ampoules should be stored in a dark place.

REVIEW QUESTIONS

1. What chemical properties does ascorbic acid exhibit?
2. Why does ascorbic acid have four stereoisomers?
3. Which ascorbic acid isomer has the highest physiological activity?
4. What are the acidic properties of ascorbic acid due to?
5. How can one explain the oxidation of ascorbic acid?
6. Explain the oxidation-reduction ability of ascorbic acid from the chemical viewpoint.
7. What chemical properties of ascorbic acid are used for its identification and quantitative determination?
8. Why should ascorbic acid solutions not be stored for a long time and why is sodium metabisulphite added to them?
9. What explains the amphoteric properties of nicotinic acid?
10. Explain the role in the human organism of the vitamins C, B₆, and nicotinamide (PP factor) (give a substantiation for each vitamin separately proceeding from its chemical properties).
11. What chemical properties of thiamine is the reaction of formation of a thiochrome based on?
12. Why can riboflavine participate in oxidation-reduction reactions?
13. What requirements must the storage of vitamin B₁₂ meet and why?

PRACTICAL LESSON

Analysis of a 5% Ascorbic Acid Solution

1. Perform identification reactions:
add two drops of a silver nitrate solution to 1 ml of a solution of the drug; a gray precipitate forms. Write the equation of the chemical reaction.
2. Conduct a quantitative analysis (iodimetry):
put 5 ml of the drug solution into a 100-ml measuring flask, add water up to the mark, agitate the mixture, transfer 5 ml of the diluted solution into a flask for titration, and titrate with a 0.1 *N* iodine solution up to a straw-yellow colour. Write the equation of the chemical reaction.
3. Evaluate the content of ascorbic acid in the solution in per cent by formula (1.2):

$$X = -\frac{VKTV_1}{aV_2} \times 100 = \frac{VK \times 0.008806 \times 100}{5.0 \times 5.0} \times 100$$

where V is the volume of the 0.1 *N* iodine solution, ml, $T = 0.008806$ g/ml, a is the volume of the drug taken for the analysis, ml, V_1 is the volume of the drug solution after the first dilution, ml, and V_2 is the volume of the aliquot part of the diluted solution taken for titration, ml.

4. Conclude whether the content of ascorbic acid corresponds to that indicated for the solution submitted for analysis.
5. Can ascorbic acid be analysed quantitatively by a different method?

Chapter 31. Antibiotics

The term **antibiotic** was first proposed by S. Waksman (USA) (from the Latin *anti*, against and *bios*, life). By this term, he understood substances formed by microorganisms and having an antimicrobial action, i.e. acting against the fundamental vital properties of microbes. Subsequently, substances having antibiotic properties were discovered in plants (phytoncids) (V. Tokin), in the blood of humans and animals (erythrin) (L. Zilber and L. Yakobson), and in other natural sources. In this connection, the concept of an antibiotic expanded, and today by antibiotics one should understand specific products of vital activities having a high physiological activity with respect to definite groups of microorganisms (viruses, bacteria, actinomycetes, fungi, algae, protozoa) or to malignant tumours, selectively retarding their growth or completely suppressing their development.

The science of antibiotics began to develop in the 1940s, when penicillin, a potent chemiotherapeutic agent against bacterial infections, was discovered.

As a result of great work performed by Soviet scientists and the medical industry of the USSR, the production of the most important antibiotics was organized during a comparatively short period.

The search for antibiotics requires the close collaboration of microbiologists (the finding of producers of new antibiotics), chemists (the isolation of active substances from the cultural liquid of the

producers), chemotherapeutists, pharmacologists, and histologists testing the physiological action of new antibiotics in experiments on animals. Here the participation of engineers and technologists having at their disposal the special equipment needed to obtain the new antibiotics in amounts required for their further study is also essential.

The development of antibiotics in the USSR is associated with the names of outstanding Soviet scientists: Z. Yermolyeva, M. Shemyakin, G. Gauze, M. Brazhnikova, A. Khokhlov, S. Navashin, and many others still working fruitfully to date.

About 3000 antibiotics are known at present, of which about 300 have a chemiotherapeutic action.

In their chemical nature, antibiotics are organic substances relating to the most diverse classes of compounds. Antibiotics, unlike other products of vital activities, have two characteristic properties:

(1) they exhibit a high biological activity with respect to organisms sensitive to them. They exhibit a high physiological action even in very small concentrations: for example, penicillin has a bactericidal action with respect to bacteria sensitive to it in a concentration of 0.000 001 g/ml;

(2) they have a selective action. Each antibiotic exhibits its action only relative to separate organisms or groups of organisms, not exhibiting a noticeable action on other forms of microorganisms. For example, penicillin retards the development of only some Gram-positive bacteria (coccus, streptococcus, etc.) and does not act on Gram-negative bacteria, fungi, or other groups of microorganisms. Thus, each antibiotic is characterized by its own specific, antimicrobial spectrum of action.

The *commercial production* of antibiotics is generally carried out by biosynthesis and has many common stages: the selection of highly productive strains and nutrient media, the process of biosynthesis, the isolation of the antibiotic from the cultural liquid, and its purification.

The intensity of biosynthesis of an antibiotic depends first of all on the properties of the producer strain. The majority of natural strains have a low activity and cannot be employed for commercial purposes. Consequently, after selecting the most active natural strain of an antibiotic producer, a variety of procedures and methods based on the laws of genetics are used to raise its productivity.

Of major importance for the biosynthesis of an antibiotic is the finding of the rational composition of the nutrient media; the latter are determined in accordance with the producer strain. Various strains have various requirements to their nutrition, therefore the composition of the nutrient media cannot be constant for all the producers.

At present, the "submerged" method is used exclusively for the commercial production of all antibiotics. This signifies that the mycelium grows in the bulk of the medium, and not only on its surface. This is achieved by continuous vigorous agitation and aeration of the medium. The air used for aeration must be sterile and supplied in very fine bubbles so that the oxygen dissolves well in the medium and is assimilated by the microorganism.

The methods of isolation and purification of antibiotics are very diverse and are determined by the chemical nature of the antibiotic. Preference is given to ion-exchange chromatography and other modern physicochemical methods.

Methods of analysis. Unlike other groups of natural compounds (alkaloids, glycosides), antibiotics have no group reactions for their qualitative identification. The latter is based on the individual chemical structure and the functional groups, which give distinguishing reactions, chiefly colour ones. Spectral analysis is widely used at present for the identification of antibiotics.

A variety of biological, chemical, and physicochemical methods are employed for the quantitative determination of antibiotics. The biological methods are based on the direct biological action of an antibiotic on a test microorganism sensitive to it. The greatest use has been found by the method of diffusion in agar with turbidimetric measurement of the concentration of the test-microbe cells forming a definite optical density of the medium (turbidity) as a result of their growth in the presence of a small amount of antibiotics. But the biological methods of control are time-consuming, and the accuracy of the analysis results depends on many external factors.

Recently, growing popularity has been gained by chemical and physical methods for the quantitative analysis of antibiotics. The greatest preference has been given to photolorimetry and spectrophotometry. They are based on the use of specific properties of the antibiotics, namely, colour reactions and the appearance or vanishing of characteristic bands in the ultraviolet or infrared regions of the spectrum under the action of various reagents (acids, alkalies, etc.).

Classification. The great diversity of the already studied antibiotics that differ greatly from one another in their biological, physical, and chemical properties has made it necessary to classify them. To date, however, there is no generally adopted viewpoint on this matter, and the approaches to the classification of the antibiotics are meanwhile determined by the professional interests of scientists. Biologists studying the producers of antibiotic substances and the conditions of their formation find it best to adopt a biological classification with a view to the biological origin of the antibiotics. Chemists involved in antibiotics synthesis consider a chemical classi-

fication of the chemical structure of the antibiotics to be most expedient.

As a result, two main types of classification, i.e. biological and chemical, prevail in the literature.

In accordance with the chemical classification proposed by M. Shemyakin, A. Khokhlov, and others (1961), and taking into account later information, the antibiotics known at present can be combined into the following groups: antibiotics of the acyclic series (fatty acids, acetylenes, polyenes, sulphur- and nitrogen-containing compounds); antibiotics of the alicyclic series [derivatives of cyclopentane (sarcomycin, etc.), cyclohexane, and of cycloheptane, and tetracyclines (compounds based on the structure of tetracycline)]; antibiotics of the aromatic series (chloromycetine, etc.); antibiotics of the heterocyclic series (penicillin, etc.); antibiotics-macrolides (erythromycin, etc.); aminoglycoside antibiotics (streptomycins, neomycins, etc.); and antibiotics-polypeptides (gramicidins, polymyxins, etc.).

31.1. DERIVATIVES OF THE HETEROCYCLIC SERIES

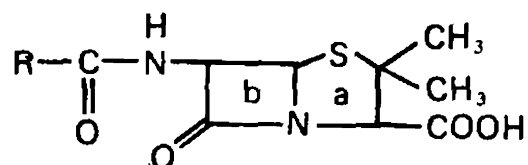
PENICILLINS (β -LACTAMIDES)

The discovery of penicillin is associated with the name of the Scottish microbiologist A. Fleming. In 1929, when growing a culture of staphylococci in his laboratory, he discovered a strain of a mould in one of the Petri dishes around which the growth of the staphylococci was delayed. Fleming isolated this fungus, i.e. mould, and discovered antibiotic properties in it. However, the healing properties of green mould were known long before Fleming's discovery to the Russian scientists V. Manasein and A. Polotebnov, who in 1871 published their observations on the healing action of green mould, named further as *Penicillium notatum*. But these discoveries found no practical development at that time, and only in 1939-1940, when penicillin was first obtained in the crystalline form, did the interest in this antibiotic grow substantially. The first penicillin was produced in the USSR in 1942 by Z. Yermolyeva. It was first introduced into medical practice at the fronts of World War II and saved the lives of thousands of Soviet soldiers.

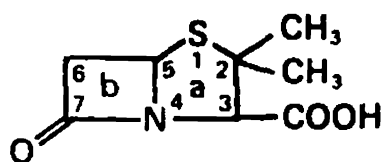
The high effectiveness of penicillin against the pathogens of a number of severe diseases made researchers intensify their search for the producents of this antibiotic.

It was found that representatives of the genus *Penicillium* are the most suitable for the commercial production of the drug. The mould fungi *Penicillium notatum* and *Penicillium chrysogenum* are the most productive strains of this genus.

The antibiotic substance produced by these moulds consists of several penicillins close in their chemical structure and having the general formula



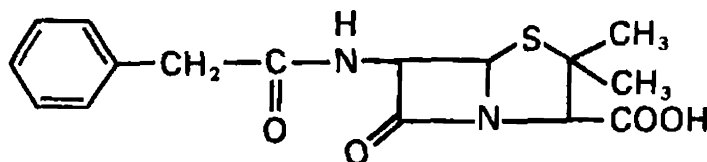
where R can vary depending on the type of penicillin. The molecule of a penicillin is based on penicillanic acid consisting of two condensed heterocyclic rings—a five-membered thiazolidine one (a) and a β -lactam one (b):



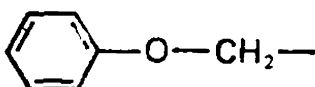
Penicillanic acid

The presence of a carboxyl group imparts strong acidic properties to a penicillin molecule, therefore penicillin readily forms salts with alkaline (Na, K) and alkaline-earth (Ca, Mg, Ba) metals, and also with organic bases such as dibenzylethylenediamine [the drug bi-cillin (benzathine penicillin)].

Position 6 of the penicillin molecule is occupied by an acylated amino group. In different penicillins, it is acylated with various acid radicals, whence the names of the penicillins originate. For example, medical penicillin, which is a derivative of phenylacetic acid, is called benzylpenicillin:

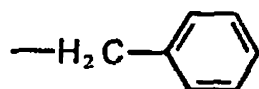


Benzylpenicillin

If R is  (phenoxymethyl), such a penicillin

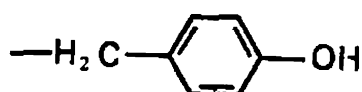
is called phenoxymethyl penicillin. The radical R can also have an aliphatic structure. Among the natural penicillins, the most frequently encountered radicals R are as follows:

$\text{H}_3\text{C}-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$ pentenylpenicillin—

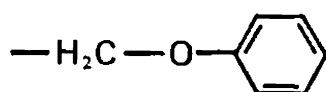
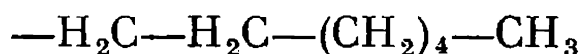


penicillin F

benzylpenicillin—penicillin Δ^2



p-hydroxybenzylpenicillin—
penicillin X



heptylpenicillin—penicillin K

phenoxymethylpenicillin—penicillin V

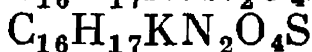
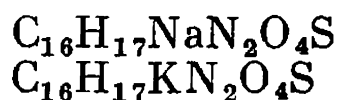
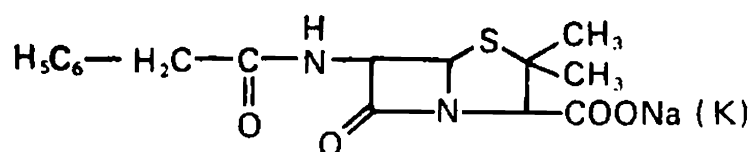
Of the greatest importance are benzylpenicillin and phenoxymethylpenicillin because they have the highest therapeutic activity. Benzylpenicillin is the main constituent part of medical penicillin.

The structure of penicillin was established according to the products of its decomposition and isomerization. Penicillin decomposes under the influence of acids, alkalies, and mercuric chloride. Its rapid destruction in their presence is due to the lactam ring (b).

Penicillin was synthesized for the first time in 1946, but the process did not gain commercial significance owing to the very low yield of the product (from 0.03 to 0.22%). To date, none of the proposed variants of penicillin synthesis can be used for its commercial production owing to the intricate nature of the process and the short supply of the starting chemical substances, and also to the very low yield of the pure product. This is why penicillin is produced exclusively by the biological method in the industry.

The medical industry of the USSR produces crystalline penicillin in the form of the sodium, potassium, and novocaine salts of benzylpenicillin, and also phenoxymethylpenicillin. All these drugs are pharmacopoeial ones.

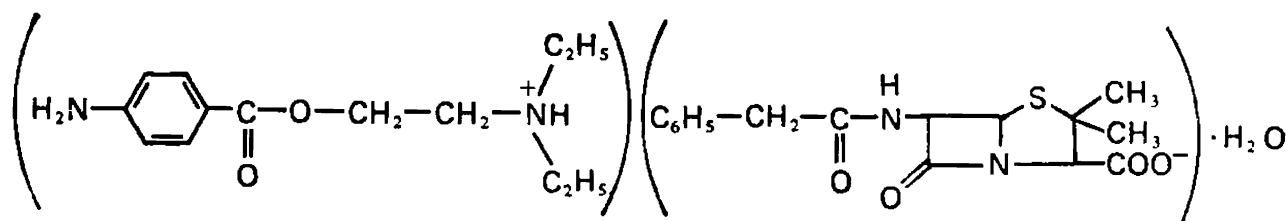
Benzylpenicillin Sodium (Potassium) Salt [(*Benzylpenicillinum-natrium (kalium)*)]



M.m. 356.38

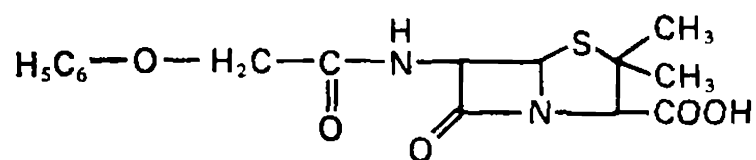
M.m. 372.49

Benzylpenicillin Novocaine (Procaine) Salt (*Benzylpenicillinum-novocainum*)



M.m. 588.70

Phenoxymethylpenicillin (*Phenoxymethylpenicillinum*)

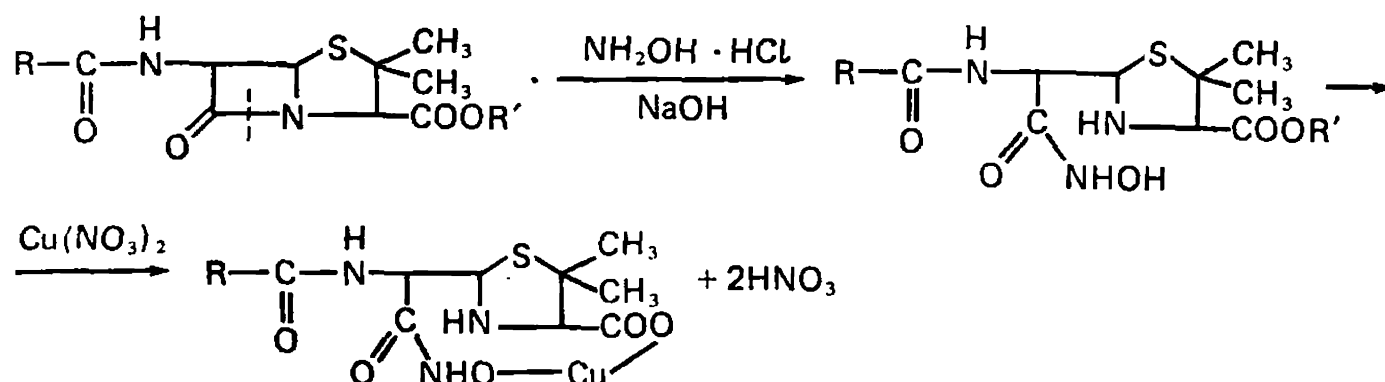

$$\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_5\text{S}$$

M.m. 350.40

All these drugs are white finely crystalline powders with a bitter taste. They decompose readily under the action of alkalis and oxidizing agents, when heated in aqueous solutions, and also under the action of the enzyme penicillinase.

Except for phenoxymethylpenicillin, they also readily decompose under the action of acids. The potassium and sodium salts of benzylpenicillin dissolve readily in water, while phenoxymethylpenicillin and the novocaine (procaine) salt of benzylpenicillin dissolve sparingly in it.

The reaction of formation of coloured hydroxamates of metals after alkaline hydrolysis (the lactam ring) in the presence of hydroxylamine chloride and the following addition of a solution of a heavy metal salt is a group reaction for penicillin drugs. For example, iron hydroxamates of a red colour are formed with iron(III) salts (FeCl_3), and copper hydroxamates of a green colour, with copper salts:



To distinguish penicillin drugs from one another, a reaction with chromotropic acid in the presence of concentrated sulphuric acid is used. Here the sodium and potassium salts of benzylpenicillin give a brown colour, phenoxymethylpenicillin gives a blue-violet colour, and the novocaine salt of benzylpenicillin—a red-brown colour (the reaction is not official).

The quality of penicillin drugs is determined by: (a) the pH of the medium potentiometrically, (b) the colour of the solution during 24 hours at 10 °C, (c) the specific rotation, and (d) the absorptivity a at a definite wavelength.

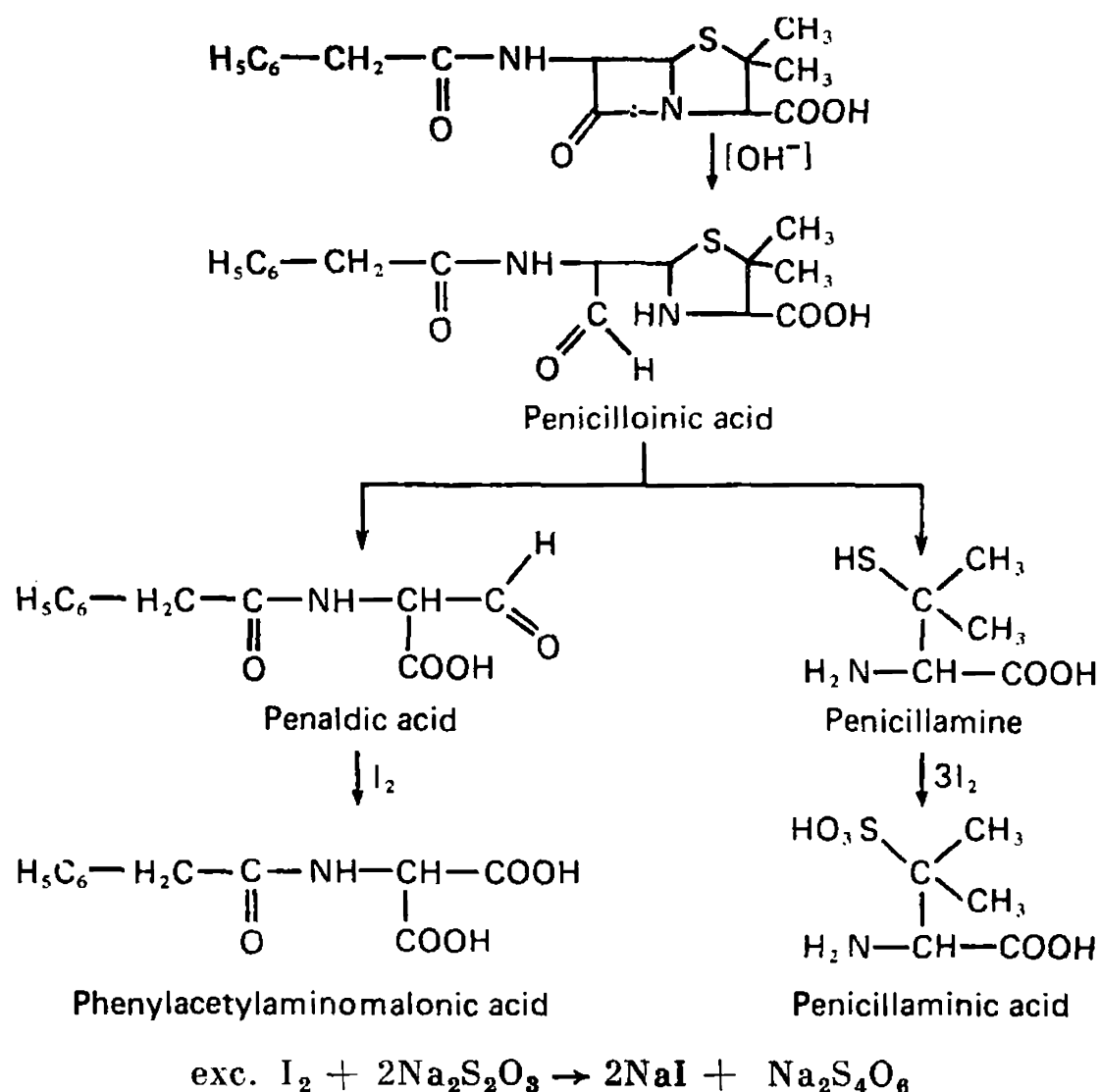
The drugs must be tested for toxicity, pyrogenic properties, and sterility, which are established by biological procedures.

Methods of quantitative analysis. Like the other antibiotics, the activity of penicillin drugs is determined by biological, chemical, and physicochemical methods.

Of the chemical methods, iodimetry after the alkaline hydrolysis of the drugs is the most widespread.

The quantitative analysis of penicillin drugs consists in:

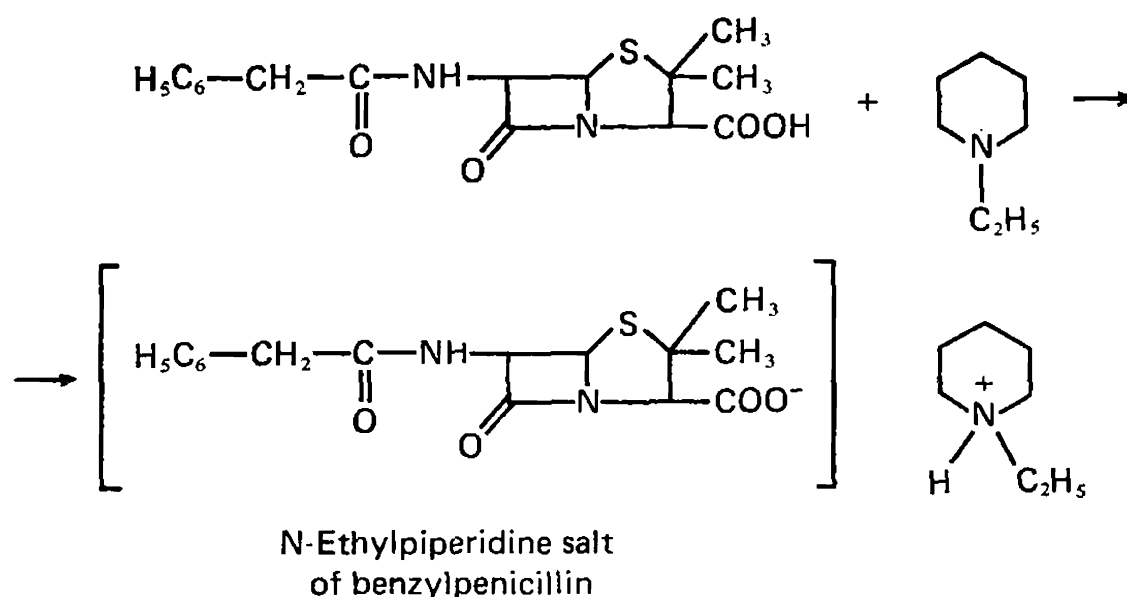
1. Iodimetric determination of the sum of the penicillins after the drugs have been hydrolyzed with an alkali (for all penicillin drugs). Since penicillin itself is not oxidized by iodine, but the products of its alkaline hydrolysis are oxidized, a weighed sample of the drug is preliminarily treated with an alkali and left at room temperature for about 20 minutes. The resulting penicillaminic acid decomposes into penaldic acid and penicillamine, and it is exactly the latter two substances that are oxidized by an iodine solution added to the reaction mixture in excess. Depending on the pH of the medium, eight or nine iodine equivalents are spent on the oxidation. An acetate buffer is employed to create a pH of 4.5 (in this case eight iodine equivalents are spent):



Simultaneously, a control test is run, i.e. an excess of a titrated iodine solution and an acetate buffer solution are added to another

portion of the drug. As in alkaline hydrolysis, 20 minutes later the excess iodine is titrated with sodium thiosulphate. The difference in the volumes of the sodium thiosulphate for the two titrations corresponds to the content of the sum of the penicillins in the drug.

2. Benzylpenicillin in drugs containing its potassium, sodium, and novocaine (procaine) salts is determined by the gravimetric method based on the formation of the N-ethylpiperidine salt of benzylpenicillin (the gravimetric form):



For the novocaine salt of benzylpenicillin, the State Pharmacopoeia requires that novocaine (procaine) be determined by neutralization in addition to the above two analyses. For this purpose, a sodium carbonate solution is added to the drug and the novocaine base precipitates, which is extracted with chloroform. An excess of acid is added to the chloroform solution of the novocaine base. The acidic aqueous layer is separated, and the excess acid is titrated with an alkali solution (the drug should contain at least 37.5 and at most 40.5 % of novocaine).

Phenoxymethylpenicillin is analysed quantitatively in two steps:

1. The sum of the penicillins is determined by iodimetry preceded by alkaline hydrolysis.

2. Phenoxymethylpenicillin is determined by spectrophotometry (the solvent is a 5% sodium hydrogen carbonate solution at $\lambda_{\text{max}} = 268 \text{ nm}$).

Of the physicochemical methods for the quantitative analysis of penicillin drugs, preference has been given to photolorimetry based on the formation of coloured hydroxamates. Methods of chromatographic analysis of penicillin have also been developed that are employed to determine the content of various types of penicillin in a mixture.

The concentration of penicillin is generally expressed in activity units. One milligramme of the sodium salt of benzylpenicillin contains 1667 units, and one milligramme of the potassium salt contains 1600 units.

The stability of penicillin varies depending on its state of aggregation. Penicillin drugs are very unstable in aqueous solutions, especially when heated. The opening of the β -lactam ring leads to inactivation of penicillin. This process also depends on the pH of the medium. This is why, for example, the potassium (sodium) salt of benzylpenicillin is produced and stored in the crystalline form in bottles hermetically sealed with rubber stoppers secured by aluminium caps. Penicillin is dispensed in bottles containing from 125 000 to 1 000 000 units. Penicillin drugs, except for phenoxymethylpenicillin, are administered intramuscularly or subcutaneously in the form of solutions. The latter are prepared *ex tempore* with a sterile isotonic solution of sodium chloride or with water. Frequently, the action of the drug is prolonged by preparing the solutions with 0.25, 0.5, or 1% novocaine (procaine) solutions.

Phenoxymethylpenicillin is stable to the action of acids. It can therefore be taken orally in tablets (it does not decompose in the acidic medium of gastric juice).

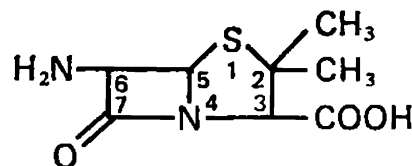
Penicillin drugs are widely used in the treatment of infections, various inflammatory and suppurative processes in the lungs, and tonsillitis. Penicillin is also used for treating some kinds of tuberculosis, pneumonia, septic endocarditis, and so on. It is employed in surgery and gynaecology.

All penicillin drugs are listed in Group B.

SEMISYNTHETIC PENICILLINS

Benzylpenicillin produced by biosynthesis and the numerous drugs created on its basis, notwithstanding the merits of their physiological action, are not deprived of shortcomings. The main one is that when the drug is used for a long time, many strains of microbes, especially staphylococcus, begin to exhibit stability to this antibiotic. This made it necessary to obtain new types of penicillin, i.e. semisynthetic drugs, which were found to be active with respect to the staphylococcus resistant to penicillin.

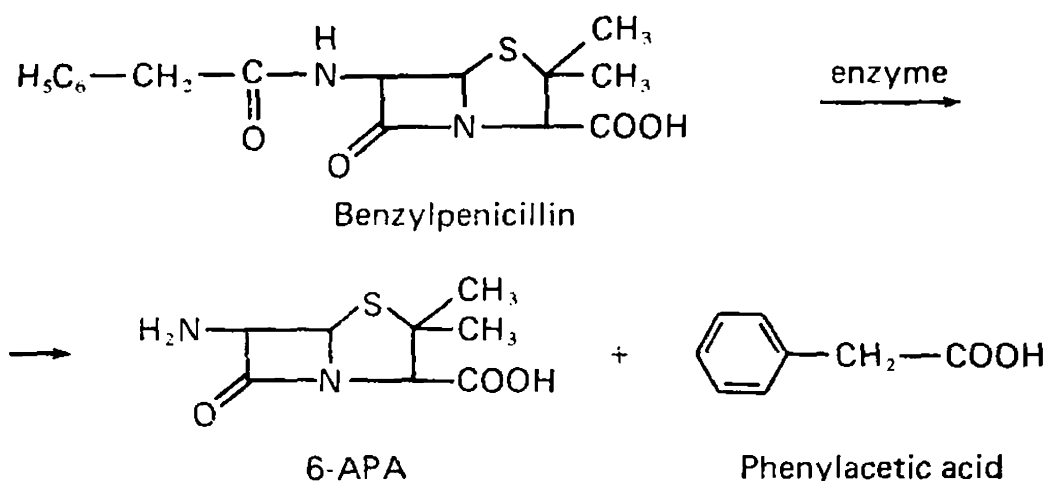
The development of this group of penicillins became possible after it was discovered (1962) that in addition to the known natural penicillins, the micelium *Penicillium chrysogenum* simultaneously contains 6-aminopenicillanic acid (6-APA), and the latter began to be used as the starting substance for the production of semisynthetic penicillins:



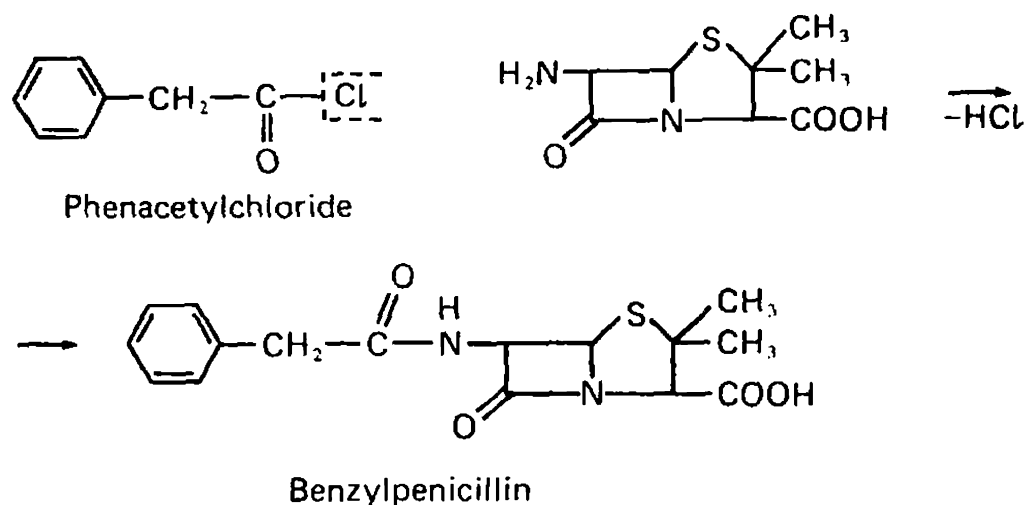
6-Aminopenicillanic
acid (6-APA)

This acid is produced by biosynthesis in two ways:

- (1) in development of the mould fungus *Penicillium chrysogenum*;
- (2) in the enzymatic hydrolysis of benzylpenicillin:



After the biosynthetic production of 6-APA, an acyl (acid) residue is introduced into it by the conventional methods of organic chemistry, a new penicillin being produced each time. For example, the treatment of 6-APA with phenylacetylchloride yields a substance identical to benzylpenicillin:

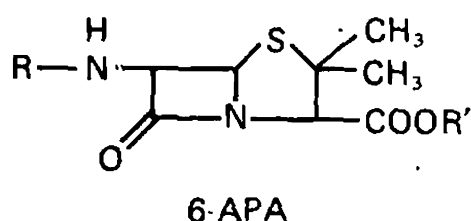


A similar reaction with phenoxyacetylchloride transforms 6-APA into a substance identical to natural phenoxymethylpenicillin, and so on. Hence, using 6-APA and various chemical compounds as the second condensing component, a large number of semisynthetic analogues of the natural penicillins were produced, as well as their modified derivatives.

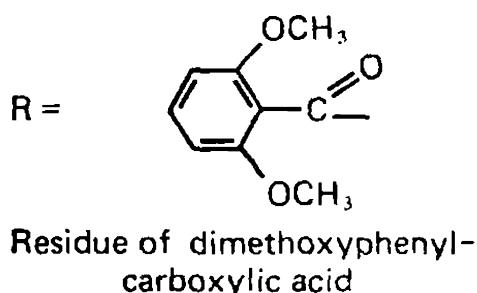
When creating the semisynthetic penicillins, the task was posed of producing drugs (1) not sensitive to the action of penicillinase, (the latter is produced by a number of bacteria) because it decomposes, i.e. inactivates penicillin; (2) resistant to acids; and (3) having a broader spectrum of action than benzylpenicillin.

With a view to these requirements, of the greatest interest among the semisynthetic penicillins are meticillin (not sensitive to the

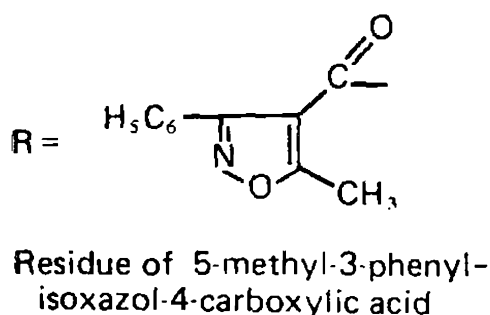
action of penicillinase), oxacillin (acid-resistant and therefore prescribed for oral administration), and ampicillin (having a broad spectrum of action). Their common structural formula is:



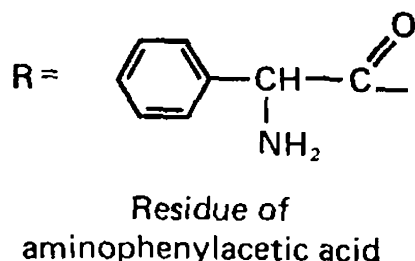
where



and R' is Na—the sodium salt of
meticillin (*Methicillinum-natrium*)



and R' is Na—the sodium salt of
oxacillin (*Oxacillinum-natrium*)



and R' is H—ampicillin (*Ampicillinum*)

All the drugs are white crystalline powders and except ampicillin dissolve well in water. They are dispensed in hermetically sealed bottles like penicillin (the sodium salts of meticillin and oxacillin) and in tablets (ampicillin and the sodium salt of oxacillin).

All the drugs are listed in Group B.

31.2. DERIVATIVES OF THE AMINOGLYCOSIDES

This group of antibiotics combines biologically active compounds containing glycoside bonds in their molecules. They include streptomycins, neomycins, and kanamycins.

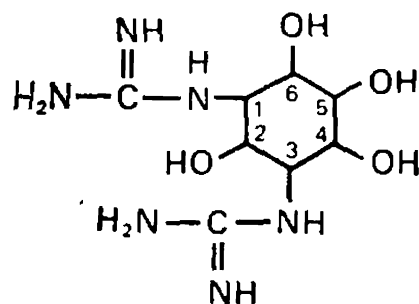
Streptomycins. Streptomycin was the second antibiotic, after penicillin, that played a very important role in the treatment of infections, especially tuberculosis.

Streptomycin was discovered by S. Waksman and his co-workers (USA) in 1944 and was named after the genus name of the actinomycetes (ray fungi) *Streptomyces*. According to Waksman, the producer of streptomycin is the actinomycete *Streptomyces griseus*.

Soviet researchers (N. Krasilnikov, 1949) relate the culture of the actinomycete forming streptomycin to *Act. globisporus streptomycini*. It was later proposed to call the organism forming streptomycin *Act. streptomycini*. Other actinomycetes forming antibiotics close to streptomycin such as oxystreptomycin were discovered subsequently.

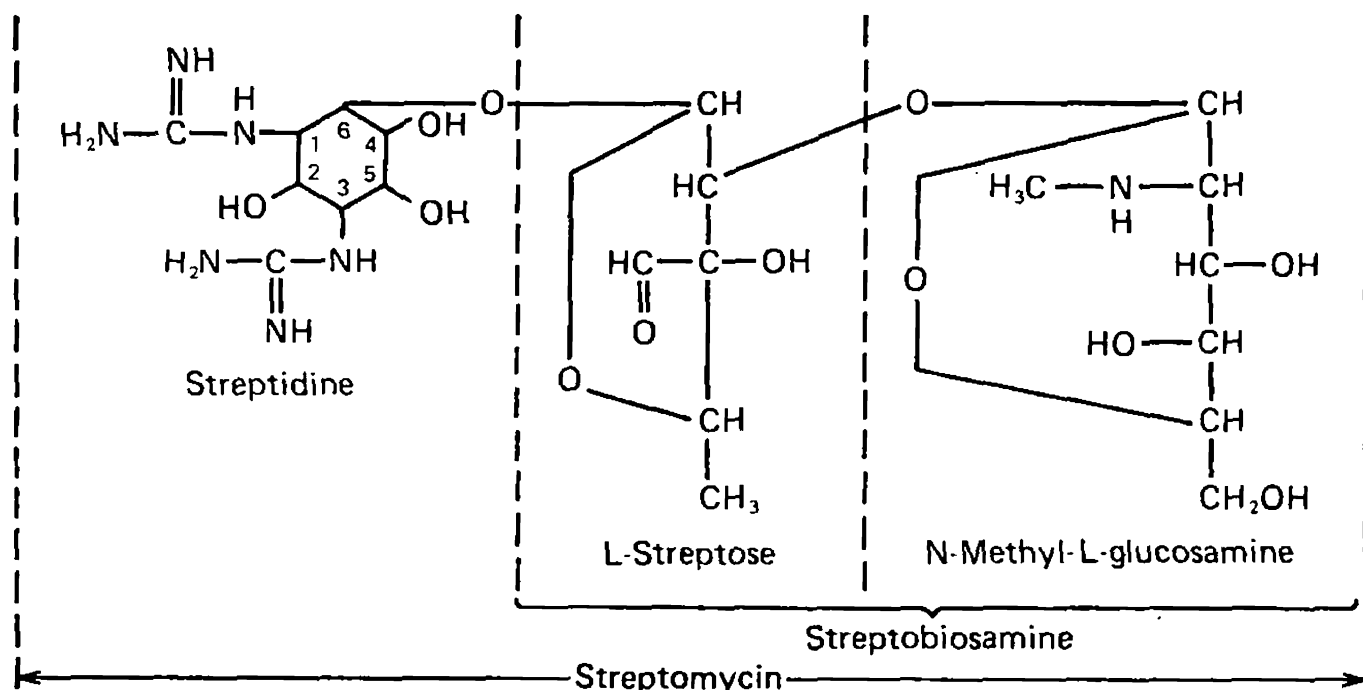
Streptomycin is the name of a group of compounds with a similar chemical structure. The streptomycin complex includes the following natural compounds: streptomycin, mannosidostreptomycin, oxystreptomycin, and also compounds produced by reduction of the first two, i.e. dihydrostreptomycin and dihydromannosidostreptomycin.

In acidic and alkaline hydrolysis, all the streptomycins evolve streptidine, which is 1,3-diguanidino-2,4,5,6-tetrahydroxycyclohexane, and the corresponding saccharide component:



Streptidine is the common part of all the streptomycin molecules.

The streptomycins differ in the nature of the saccharide component of the molecule. For example, in streptomycin, the streptidine is joined by a glycoside bond to the disaccharide streptobiosamine consisting of L-streptose and N-methyl-L-glucosamine:



Mannosidostreptomycin repeats the structure of streptomycin and differs from it only in an additional saccharide, i.e. D-mannose, which is joined by a glycoside bond to N-methyl-L-glucosamine, and so on.

Of the natural varieties of streptomycin, only streptomycin proper has found use in medicine; its derivatives either exhibit no physiological activity or are very toxic. Streptomycin, like penicillin, is produced by the biological method. Highly productive strains of the producent are obtained by selection.

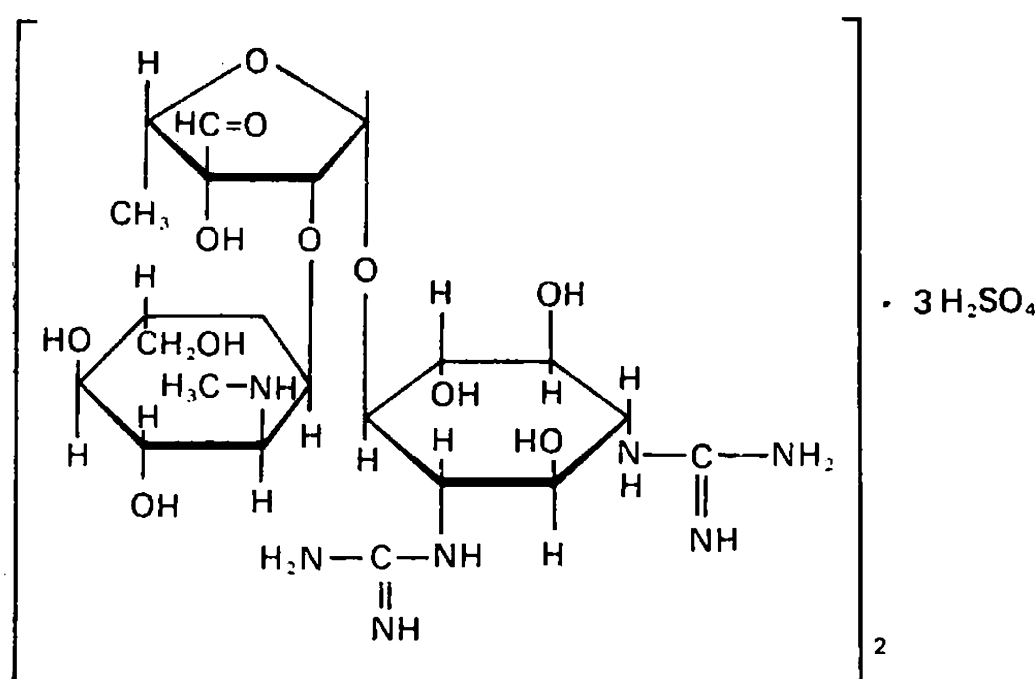
From the chemical viewpoint, streptomycin is a strong organic base. Its basic nature is due to its containing two guanidine residues and an N-methyl group of the saccharide component of the molecule.

Being a base, streptomycin readily forms salts with both mineral and organic acids. The salts are hygroscopic and readily dissolve in ethanol and other organic solvents. In the solid state, streptomycin salts can fluoresce in ultraviolet light. A typical property of streptomycin is its ability to form complexes with salts of some bivalent metals. The presence in a streptomycin molecule of a large number of hydroxyl and amine groups underlies its high hydrophilic property (solubility in water). An aqueous solution of the base has a pH of 12.0.

Streptomycin and its solutions are much more stable than penicillin. Its aqueous solutions are the most stable at a temperature below 28 °C and a pH of 7-8. The activity of the antibiotic sharply drops in an acidic medium (at a pH about 6). A weakly alkaline medium is the most favourable for streptomycin to exhibit its antibiotic action.

The streptomycin drugs used in medicine are generally its salts of sulphuric (sulphate), hydrochloric (hydrochloride), phosphoric (phosphate), and other acids. The double salt of streptomycin trichlorohydrate and calcium chloride is also employed. Streptomycin salts are more stable than its base. Pure streptomycin salts in the dry state do not lose their activity when stored during several years. The activity of streptomycin drops sharply when stored at 50 °C or even when heated for a brief period to 100-110 °C.

The pharmacopoeial preparation of streptomycin is streptomycin sulphate.

Streptomycin Sulphate (*Streptomyces sulfas*)
 $(C_{21}H_{39}N_7O_{12})_2 \cdot 3H_2SO_4$

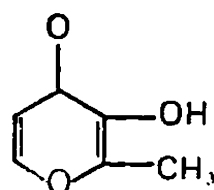
M.m. 1457.38

Streptomycin sulphate is a white powder or porous solid with a bitter taste. It dissolves readily in water, and is insoluble in alcohol, chloroform, and ether.

The identification reactions of streptomycin sulphate depend on its chemical properties and the functional groups in the molecule. The aldehyde group in the drug underlies its reducing properties. It reacts with Nessler's reagent to yield brown metallic mercury, and with Fehling's solution to yield red copper(I) oxide.

The guanidine groups in streptomycin produce a positive Sakaguchi reaction consisting in the formation of a coloured compound when a solution of 1-naphthol, 8-hydroxyquinoline, or 1-naphthol-8-sulphonic acid is added to the test streptomycin solution in an alkaline medium in the presence of an oxidizing agent. The State Pharmacopoeia recommends sodium hypobromide as the oxidizing agent; in this case a violet-red colour is observed. A typical reaction for the guanidine groups is their decomposition when heated with an alkali with the formation of ammonia.

A specific reaction for streptomycin is the formation of maltol (1-methyl-2-hydroxy-3-pyran) from the streptose part of the streptomycin molecule when it is heated with an alkali:



Maltol

Maltol yields a colour from red to violet with iron(III) salts. This reaction is recommended by the State Pharmacopoeia for identifying streptomycin. A solution of the drug is heated with an alkali in a water bath. When cooled, it is treated with a solution of ammonium iron alum in the presence of sulphuric acid. A violet colour is observed. The sulphate ion SO_4^{2-} is determined with a barium chloride solution by the formation of a white barium sulphate precipitate.

To check the purity of streptomycin drugs, it is necessary to determine the pH of 28% solutions, their transparency and lack of colour during 24 hours at a temperature not above 10 °C. The drug is tested for toxicity, pyrogenic nature, sterility, and the presence of substances with a histamine-like action.

The State Pharmacopoeia recommends determining the content of streptomycin sulphate in a drug by the biological method of diffusion in agar with the test microbe *Bacillus mycoides*.

Physicochemical methods can also be employed for the quantitative determination of streptomycin. They are based on the nature of the functional groups in the streptomycin molecule and the relevant reactions.

The maltol method is the most widespread of them. In various modifications of this method, the amount of maltol is determined either from the absorption peak in the ultraviolet region of the spectrum, or by photolorimetry. In the first case, the determinations are conducted in an acidic or alkaline medium, and the measurements are made at $\lambda = 275$ or 325 nm, respectively. In photolorimetry, iron(III) salts are used as the reagent.

Streptomycin is effective in treating the most diverse diseases caused by Gram-positive, Gram-negative, and acid-resistant bacteria. It is especially effective against the tuberculosis pathogen *Mycobacterium tuberculosis hominis*.

In addition to its high effectiveness in treating a number of diseases, streptomycin has a number of significant disadvantages, one of which is its tendency to produce streptomycin-resistant strains of organisms. This makes it necessary to increase the doses of the drug, which causes toxic effects.

The drug produces a number of undesirable side effects. It acts on the central nervous system, and results in the impairing or complete loss of hearing. Prolonged administration of the antibiotic results in various forms of dermatitis, photophobia, and great irritation of the epidermis.

Streptomycin is often prescribed in combination with other antituberculosis drugs such as PAS-Na and ftivazide.

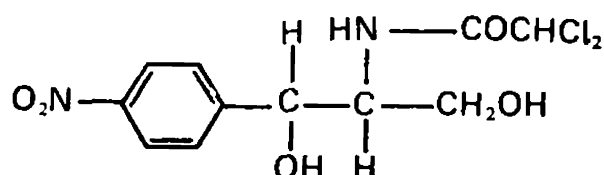
Streptomycin drugs are administered intramuscularly most frequently. They are dispensed in bottles hermetically closed with rubber plugs and protected by metal caps. They are stored in a dry place at room temperature. They are listed in Group B.

31.3. DERIVATIVES OF THE AROMATIC SERIES

The antibiotics related to this group are mainly benzene derivatives. A representative of these antibiotics is chloramphenicol, a natural antibiotic, and its synthetic analogue levomycetin.

Levomycetin (Chloramphenicol) [*Laevomycetinum (Chloramphenicolum)*]

D-(—)-*threo*-2-(dichloroacetamido)-1-(*p*-nitrophenyl)-1,3-propanediol



$C_{11}H_{12}Cl_2N_2O_5$

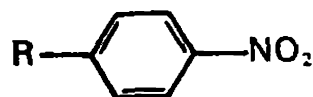
M.m. 323.13

Chloramphenicol is produced by the soil actinomycete *Act. Streptomyces venezuelae*. The strain of this producent was first isolated from the soils of Venezuela (1947), which explains its name.

Chloramphenicol is an antibiotic with a broad spectrum of action. It acts not only against Gram-positive and Gram-negative bacteria, but also against Rickettsia that are pathogens of abdominalis typhus, spotted fever, brucellosis, and cholera. These diseases could not be cured with the previously known antibiotics and other drugs.

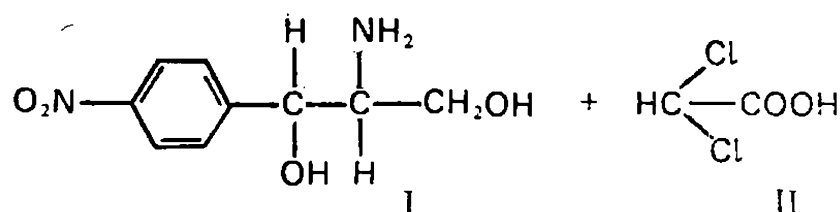
Such a broad range of action of the antibiotic attracted great attention of investigators to it, and during two years not only was its chemical structure studied, but it was synthesized (1949, USA).

Almost at the same time in the USSR, academician M. Shemyakin and his co-workers synthesized analogues of chloramphenicol and studied the relation between its structure and antibiotic action. The biological activity of chloramphenicol was found to depend very greatly on the space configuration of the molecule. Spectral analysis revealed that chloramphenicol belongs to the derivatives of para-substituted nitrobenzenes:

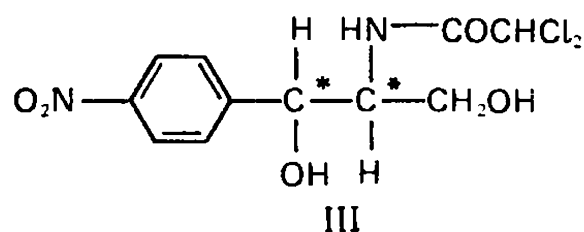


The hydrolysis of chloramphenicol yields a compound containing an amino group—the base of chloramphenicol(I) and dichloroacetic

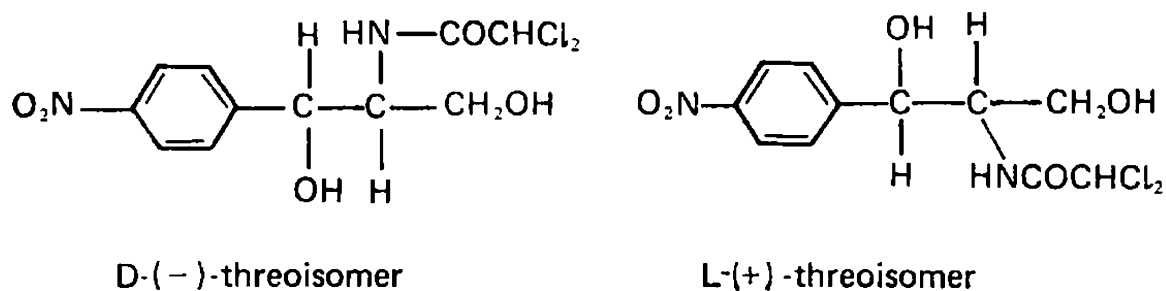
acid (II):



The condensation of the products again yields chloramphenicol (III) whose molecule is depicted structurally as follows:



Chloramphenicol has two asymmetric carbon atoms, therefore four stereoisomers or two pairs of antipodes can exist, namely, D (—) and L (+) threo isomers (with a *trans* structure), and D (—) and L (+) erythro isomers (with a *cis* structure*). They differ in the space arrangement of the OH and H groups at the first carbon atom of the side chain:



Both isomers of the erythroform are very toxic and are not used in medicine.

The synthesis of chloramphenicol was the first chemical synthesis of an antibiotic embodied on an industrial scale, and to date this is one of the few antibiotics produced by chemical synthesis.

The chemical synthesis of chloramphenicol yields a racemic preparation, i.e. a compound containing the L (+) and D (—) threo-

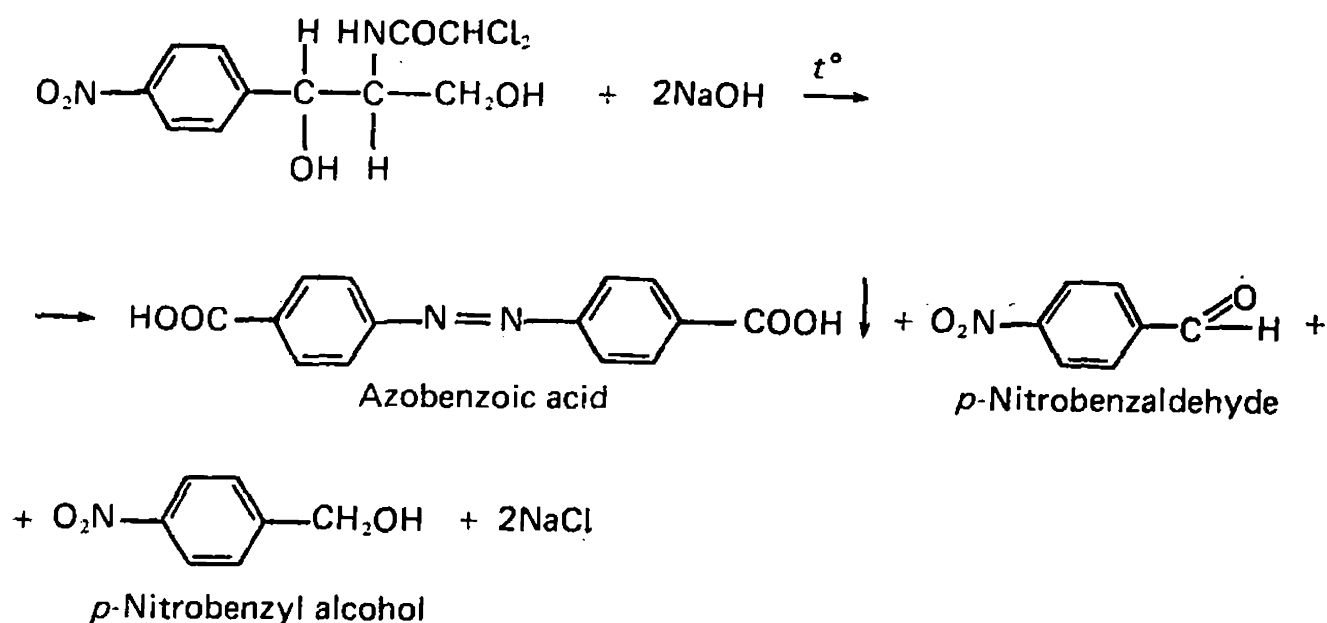
* With a view to the configuration of an asymmetric carbon atom in position 1, optically active compounds are related to the D or L series. Since the optical activity depends on the configuration at all asymmetric carbon atoms, there can be levo- and dextrorotatory isomers in both the D and the L series. The sign of right-hand (dextro) (+) or left-hand (levo) (—) rotation of the plane of a polarized ray is indicated in parentheses after the designation of the configuration (D, L).

forms of chloramphenicol. The racemic preparation synthesized by Soviet chemists was named synthomycin (DL-chloramphenicol). Later, its levorotatory isomer, the D (—) threoform, was isolated from synthomycin, and was called levomycetin.

The biological activity of synthomycin is half that of levomycetin and therefore synthomycin is not employed in medicine at present. Levomycetin and levomycetin stearate are the pharmacopoeial preparations.

Levomycetin is a white odourless crystalline powder, sometimes with a slightly yellowish-green tint. It has a bitter taste. It dissolves sparingly in water, readily in alcohol, and does not dissolve in chloroform.

To identify the drug, the State Pharmacopoeia recommends a reaction with an alkali attended by heating. First a yellow colour appears that turns red-orange with further heating. The colour becomes more intense when the solution is boiled, and a brick red precipitate appears owing to the formation of azobenzoic acid. In addition, *para*-nitrobenzaldehyde and *para*-nitrobenzyl alcohol form:

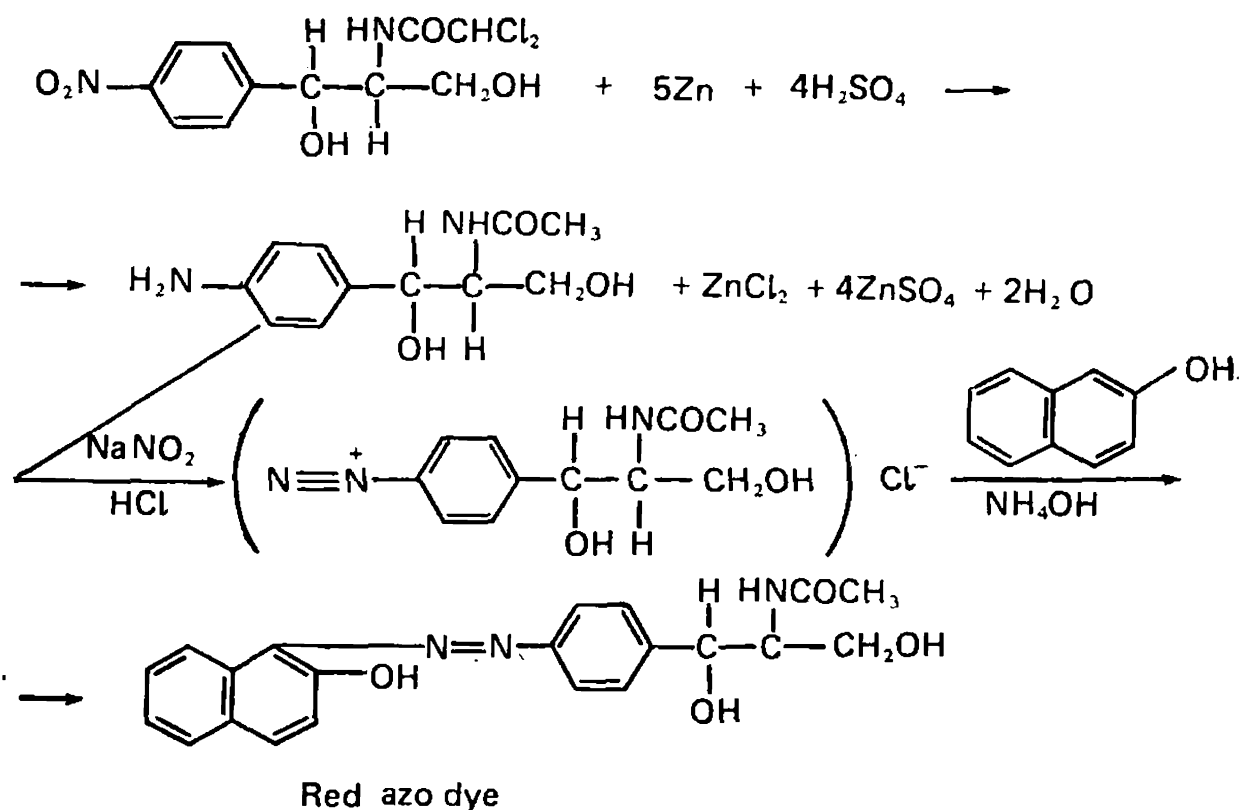


After separation of the precipitate, the filtrate is acidified with nitric acid, and the Cl^- ion is determined in it by adding a silver nitrate solution.

When the drug is boiled with an alkali (NaOH), the dichloroacetic acid detaches chlorine, which forms sodium chloride in the alkaline medium. The chloride yields a white curdy precipitate of silver chloride with a silver nitrate solution.

Levomycetin is an optically active compound, hence it is characterized by a specific rotation. The latter should range from $+18$ to $+21^\circ$ (a 5% solution in 95% alcohol). It must be noted that a solution of the drug in ethyl acetate rotates the plane of a polarized ray to the left, and an alcohol solution, to the right.

Levomycesin can also be identified by other reactions, for example, its reduction to an aminoderivative. The latter is diazotized and couples in the alkaline medium with 2-naphthol to form a red azo dye:



The State Pharmacopoeia recommends determining the content of levomycesin in the drug by nitritometry after reduction (with heating) of the nitro group by zinc dust in the presence of hydrochloric acid (see Chap. 23).

Other methods of analysis have also been proposed that are based on the chemical properties of the drug, namely, bromatometry (the aromatic ring is brominated), colorimetry (based on the formation of azo dyes after reduction of the nitro group), and argentometry (determination of the chloride ion after alkaline hydrolysis). Of the physicochemical methods, spectrophotometry and polarimetry can be employed.

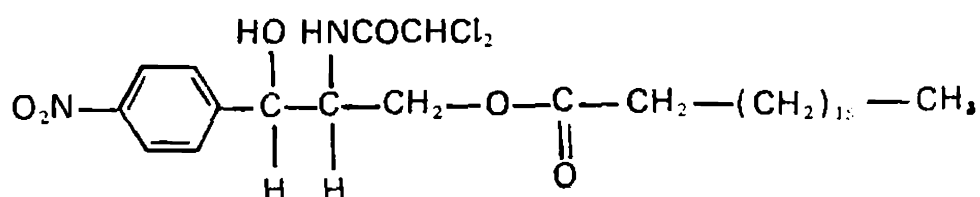
Levomycesin is employed in the treatment of abdominalis typhus and paratyphoid fever, dysentery, brucellosis, whooping-cough, tularaemia, gonorrhoea, spotted fever, and other diseases caused by viruses. Prolonged treatment with levomycesin may cause fungal diseases of the skin and mucous membranes of the mouth, pharynx (thrush), rash, dermatitis.

The drug is prescribed for oral administration. It is dispensed in powders, coated tablets, capsules, in the form of suppositories, and a 1% ointment.

A shortcoming of levomycesin is its bitter taste, which restricts its use, for example, for children. It can be eliminated by transform-

ing the antibiotic into various esters. Esters of levomycetin have been obtained with carbonic, sulphuric, palmitic, stearic, succinic, and other acids. Of these, levomycetin stearate is used in medicine and is a pharmacopoeial drug.

Levomycetin Stearate (*Laevomycetini stearas*)
D-(—)-threo-2-(dichloroacetamido)-1-(p-nitrophenyl)-1,3,3-
propanediol stearate



$\text{C}_{29}\text{H}_{46}\text{Cl}_2\text{N}_2\text{O}_6$

M.m. 589.60

The antibiotic effect of the drug is due to the active levomycetin, which is liberated from the ester as a result of fermentative hydrolysis in the alimentary tract after the drug has been taken orally.

Levomycetin stearate is a white powder with a yellowish tint. It is insoluble in water, dissolves sparingly in alcohol, and readily in chloroform and acetone. Its solutions in all cases are turbid.

Levomycetin stearate participates in all the reactions characteristic of levomycetin. A distinguishing reaction is the formation of oily drops of stearic acid evolved in hydrolysis after the drug is heated with concentrated hydrochloric acid. When the reaction mixture is cooled, the oily drops of stearic acid on the surface of the liquid solidify. The content of levomycetin stearate is determined spectrophotometrically (State Pharmacopoeia).

The indications for administration are the same as for levomycetin. The drug has side effects similar to those of levomycetin. It is dispensed in powders, tablets, granules, and in the form of a 5% suspension.

It should be stored in well closed containers or orange glass jars. It is listed in group B.

31.4. DERIVATIVES OF THE ALICYCLIC SERIES

TETRACYCLINES

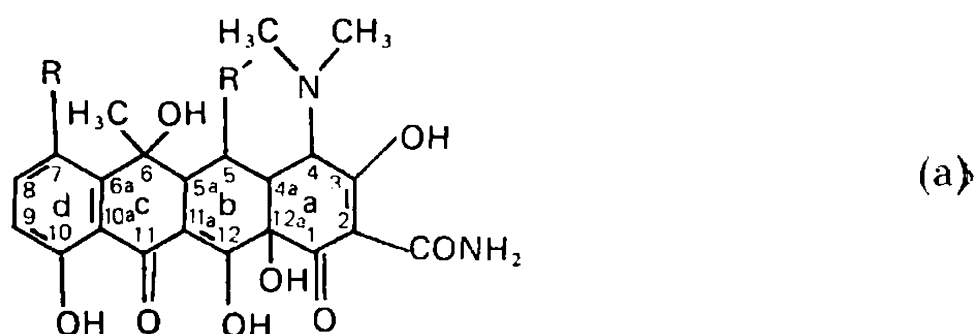
The antibiotics of the tetracycline series occupy a leading place among antibiotics with a broad spectrum of action. They suppress the reproduction of Gram-positive and Gram-negative microorganisms, acid-resistant bacilli, Rickettsia, and large viruses.

Owing to such a broad spectrum of action, they are employed for the treatment of pneumonia, brucellosis, tularaemia, whooping-

cough, scarlatina, dysentery, spotted fever, and other diseases, for example, gastric ones.

The tetracycline antibiotics combine a high biological activity with a relatively low toxicity.

The chemical structure of the tetracycline antibiotics is based on hydronaphthacene—a condensed system of four partially hydrogenated fused benzene rings. These antibiotics differ only in the substituent in positions 5 and 7, which can be seen from the following chemical structure of a tetracycline molecule:



When $R = \text{Cl}$ and $R' = \text{H}$, the compound is chlorotetracycline (biomycin, aureomycin); when $R = \text{H}$ and $R' = \text{OH}$, it is oxytetracycline (terramycin); and when $R = \text{H}$ and $R' = \text{H}$, it is tetracycline.

At present, about 34 compounds belong to the tetracycline antibiotics and their related compounds formed in the process of biosynthesis. The most widely known tetracycline antibiotics in addition to those indicated above are 6-demethyltetracycline (a methyl group is absent in position 6), 7-chloro-6-demethylchlorotetracycline, 7-bromotetracycline, and also metacycline and doxycycline produced as a result of the chemical modification of the oxytetracycline molecule.

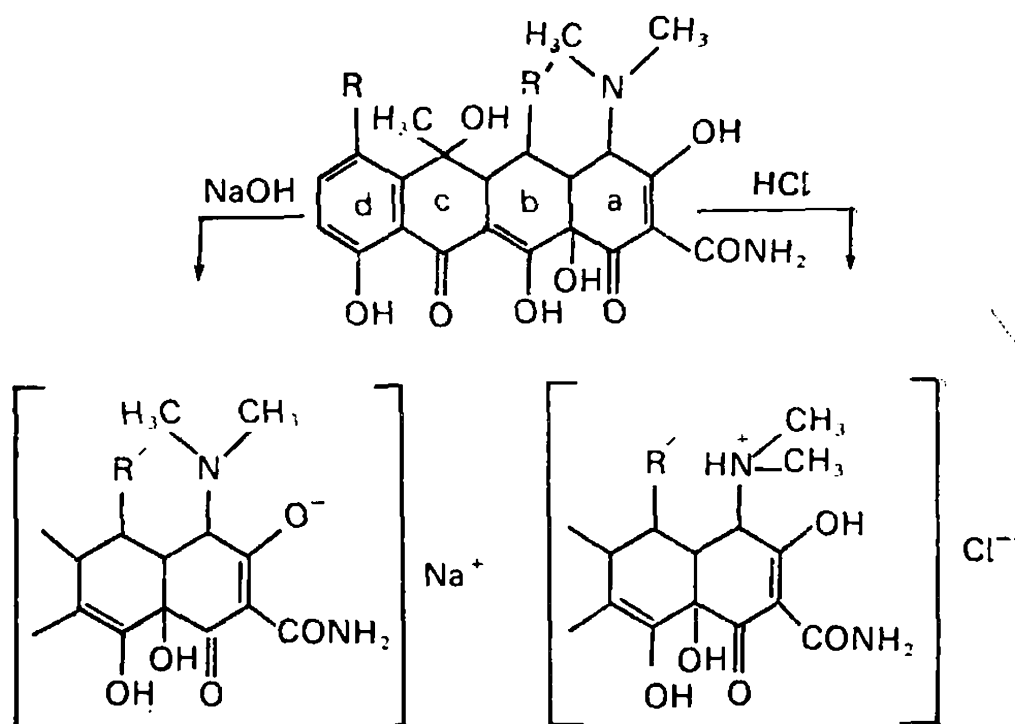
The antibiotics of the tetracycline series have received attention since 1948. The first to be discovered was 7-chlorotetracycline—aureomycin, produced by the soil actinomycete *Act. Streptomyces aureofaciens* having a gold colour, whence the name of this antibiotic. In 1952, an analogue of aureomycin was produced in the USSR and was named biomycin. Next other antibiotics of this series were discovered.

With a view to the difficulties involved in the synthesis of the tetracyclines, to date they are produced commercially by biosynthesis. The tetracyclines are close in their chemical structure, therefore their properties are also quite similar in many respects [see formula (a)].

All the antibiotics of the tetracycline series are amphoteric. Their basic properties are due to the dimethylamino group $-\text{N} \begin{matrix} \text{CH}_3 \\ \text{CH}_3 \end{matrix}$.

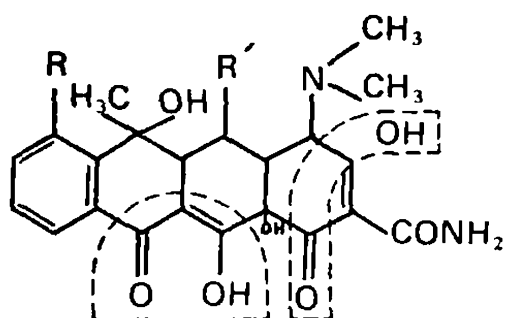
Their acidic properties are due to the phenol hydroxyl group in ring d and chiefly to the enol groups (positions 12 and 3). The strongest acidic properties are exhibited by the enol group in position 3.

Being amphoteric substances, the tetracyclines dissolve in alkalies and acids with the formation of salts:



Aqueous solutions of the tetracycline salts hydrolyze, and when concentrated solutions are left standing, a precipitate of the base appears. An excess of an acid prevents hydrolysis and the precipitation of the base.

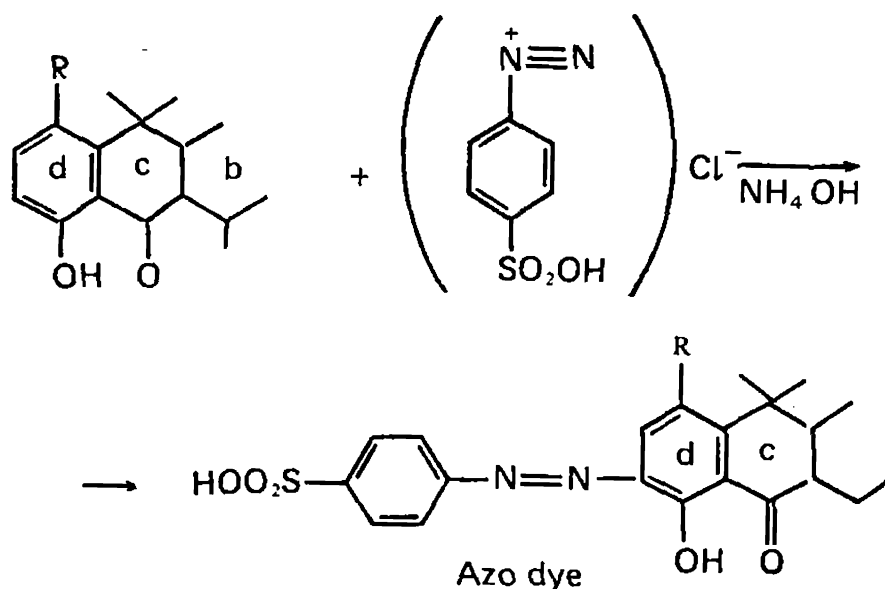
The presence in a tetracycline molecule of two systems of conjugate double bonds including keto and enol groups (enclosed by dashed lines) underlies the colour of these compounds and the characteristic absorption in ultraviolet light:



All the tetracyclines have similar spectra.

The phenol hydroxyl group in a tetracycline molecule causes a colour to appear in a reaction with iron(III) chloride and an azo dye

to form when coupled with diazonium salts:



A feature of tetracyclines is their decomposition by an alkali with the formation of isotetracyclines, whose colour is more intense than that of the antibiotic itself.

In addition to the group reactions characteristic of all the tetracyclines [a reaction with an iron(III) chloride solution, decomposition by alkalies, the formation of an azo dye], they can be distinguished from one another by their different colour when reacted with concentrated sulphuric acid. The products are anhydrotetracyclines having a definite colour for each tetracycline compound. For example, when the initial compound is oxytetracycline, a purple-red colour appears, and when it is tetracycline proper—a violet one (State Pharmacopoeia).

All the tetracyclines fluoresce in ultraviolet light, which is employed to identify them.

Oxytetracycline Hydrochloride (*Oxytetracyclini hydrochloridum*)

$\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_9 \cdot \text{HCl}$

M.m. 496.90

Oxytetracycline Dihydrate (Terramycin) (*Oxytetracyclini dihydras*)

$\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_9 \cdot 2\text{H}_2\text{O}$

M.m. 496.50

Tetracycline Hydrochloride
(*Tetracyclini hydrochloridum*)

 $C_{22}H_{24}N_2O_8 \cdot HCl$

M.m. 480.90

Tetracycline (*Tetracyclinum*)

 $C_{22}H_{24}N_2O_8$

M.m. 444.40

All these drugs are yellow odourless crystalline powders with a bitter taste. They dissolve sparingly in water (except for tetracycline and oxytetracycline hydrochlorides) and very sparingly in alcohol. Salts of the tetracyclines when left in the air become turbid owing to the gradual precipitation of the bases. In storage, the drugs gradually turn dark because they are oxidized by the oxygen of the air. This occurs most readily in aqueous alkaline solutions, which rapidly darken in the air.

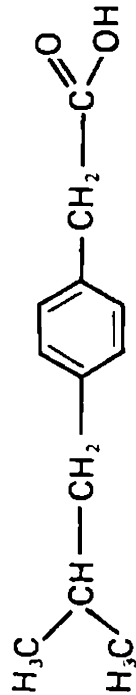
The quality of the drugs is determined by their physicochemical properties, namely, the specific rotation and the absorptivity. The acidity or alkalinity of solutions of the drugs is determined.

The State Pharmacopoeia recommends the biological method for the quantitative analysis of drugs of the tetracycline series. But other methods can also be employed such as fluorometry, photocolourimetry, spectrophotometry, and acid-base titration in non-aqueous media.

The drugs are prescribed in the form of powders and tablets, or of ointments for external application. They should be stored in a dry place protected from light at room temperature. They are listed in Group B.

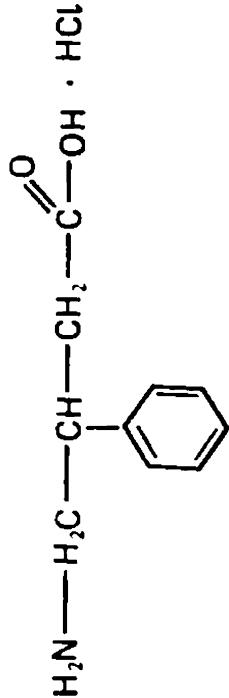
REVIEW QUESTIONS

1. Which compounds are called antibiotics?
2. What has been adopted as the unit of antibiotic activity?
3. Name the rings forming the basis of a penicillin molecule.
4. What explains the ability of penicillin to form salts?
5. What property of penicillin drugs is responsible for their group identification reaction?
6. Compare the structure of preparations of penicillin and semisynthetic penicillins, and trace the change in their physical and chemical properties. How do the pharmacological properties change in this connection?
7. What compounds does the streptomycin complex include?
8. Compare the pharmacological action of penicillins, streptomycins, and levomycetin.
9. What nucleus is the tetracycline molecule based on?
10. What are the amphoteric properties of tetracyclines due to?
11. What happens to tetracycline molecules when they react with an alkali, an acid, and with salts of the heavy metals?



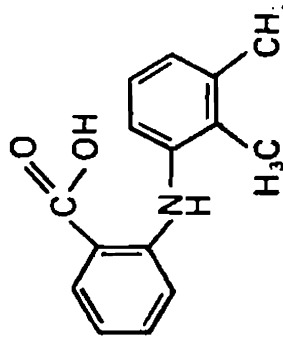
Colourless crystals

4. Phenibut (*Phenibutum*)



White crystalline powder may have slightly yellowish tint

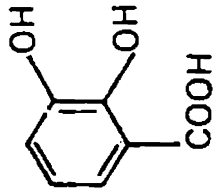
5. Mephenamic acid (*Acidum mephenamicum*)



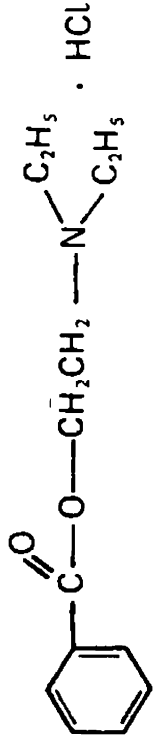
Grayish-white crystalline powder

should have a definite wavelength peak	matoid arthritis, neuralgia, myalgia)	
Add a ninhydrin solution, a blue-violet colour appears (an amino acid)	Tranquilizer (nervous, psychopathic states)	0.1- and 0.25-g powders and tablets
A 0.1% solution in chloroform fluoresces with a pale blue colour in UV light	Antiphlogistic, analgesic, antipyretic agent (rheumatism, neuralgia, feverish states)	0.25-g powders and tablets

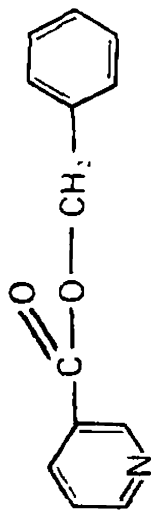
* Aqueous solutions of the drugs are generally used for the identification reactions.

Name, structure, description	Identification *	Main use	Medical form
6. Dihydroxybenzoic acid (<i>o</i>-pyrocatechuic acid) (<i>Acidum dihydrobenzoicum</i>)  Cream-coloured crystalline powder	(1) Add several drops of an iron(III) chloride solution; a blue-violet colour appears (phenol hydroxyl groups); (2) treat a small amount of the drug with ammonia water and evaporate; to the residue add a diazo reagent and a solution of 1-naphthylamine in 95% alcohol; an orange colour appears immediately that becomes more intense when left standing (phenol hydroxyls)	Antiphlogistic, antipyretic and anaesthetic agent	0.5-g tablets

Carboxylic acid esters

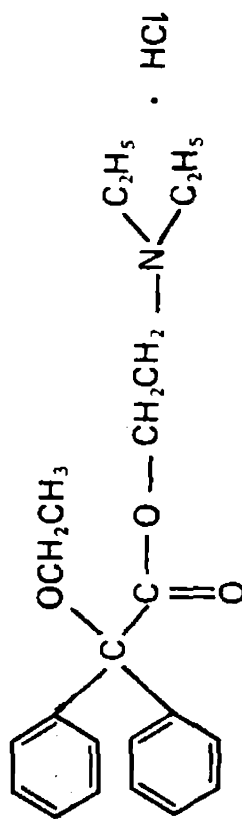
7. Bencaïne (2-diethylaminoethyl benzoate) (<i>Bencaïnium</i>)  White crystalline powder, slightly hygroscopic	(1) Add two drops of a 42% perchloric acid solution; a milky white emulsion forms that after some time becomes stratified with the separation of colourless oily drops (bencaïne base); this distinguishes the drug from novocaine (procaine); (2) a reaction with a silver nitrate solution for chlorides	For infiltration anaesthesia (in stomatology)	Powders, ampoules with 1 ml of 0.5, 1, and 2% solution
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8. Benzyl nicotinate (*Benzylnicotinat*)



Colourless or yellow transparent liquid with a typical smell

9. Estocin[®] (esthocene, dimenoxadol) (*Aesthocinum*)



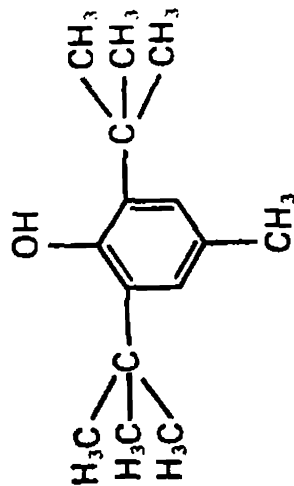
White crystalline powder

(1) Add anhydrous sodium carbonate with heating; benzaldehyde forms (a smell of bitter almonds); (2) add 1 ml of a sodium hydroxide solution to an alcohol solution of the drug and boil for 3 min; after cooling neutralize with a 1 N acetic acid solution using a phenolphthalein indicator and add several drops of a copper sulphate solution; a blue precipitate forms (the nicotinic acid residue)	Included in heparin ointment	0.005-, 0.015-, 0.03- and 0.06-g powders and ampoules with 2 ml of 2% solution
(1) In acid hydrolysis, a precipitate of diphenylacetic acid forms; after drying the precipitate, find its melting point; (2) in acid hydrolysis in the presence of hydroxylamine and the subsequent addition of an iron(III) chloride solution a coloured iron hydroxamate forms (an ester group); (3) a red colour appears with concentrated sulphuric acid in an anhydrous medium (gallochromines); the reaction proceeds in time, after hydrolysis of the ethoxy group;	Analgesic and antitussive agent. Analgesic for pains associated with spasms of the smooth muscles. Has a mild antiphlogistic action	

Name, structure, description	Identification *	Main use	Medical form
10. Spasmolytin (<i>Spasmolytinum</i>) <chem>CCN(CC)CCOC(=O)Cc1ccccc1-c2ccccc2</chem> White crystalline powder with salty and bitter taste	(4) a reaction with a silver nitrate solution for chlorides (1) Forms a coloured iron hydroxamate similar to estocin (an ester group); (2) a red colour appears with concentrated sulphuric acid in an anhydrous medium (gallochromines)	Spasmolytic agent; relaxes smooth muscles of internal organs and blood vessels, also produces local anaesthesia	0.1-g powders and coated tablets
11. Amizil (benactyzine) (<i>Amizylum</i>) <chem>CCN(CC)CCOC(=O)C(O)(c1ccccc1)c2ccccc2</chem> White crystalline powder	(1) Forms a coloured iron hydroxamate similar to estocin (an ester group); (2) a blood-red colour appears with concentrated sulphuric acid in an anhydrous medium (gallochromines); (3) a reaction with a silver nitrate solution for chlorides	Spasmolytic, cholinolytic, antihistaminic agent (Parkinson's disease, cholecystitis, spastic colitis, ulcers)	0.001-0.002-g tablets, powder (for preparing solutions)
Phenol derivatives			
12. Phethanol (etilefrine) (<i>Phethanolum</i>) <chem>CCN(CC)CCOCc1ccc(O)c(O)c1</chem>	(1) Add two drops of an iron(III) chloride solution; a violet colour appears (phenol hydroxyl); (2) to 1 mg of the drug add 2-3 drops of an am-	Adrenomimetic agent (vasoconstrictive); raises blood pressure in various hypotonic states; lowers intra-ocular	0.005-g coated tablets; 1-ml ampoules with 1% solution; powder for preparing ophthalmic

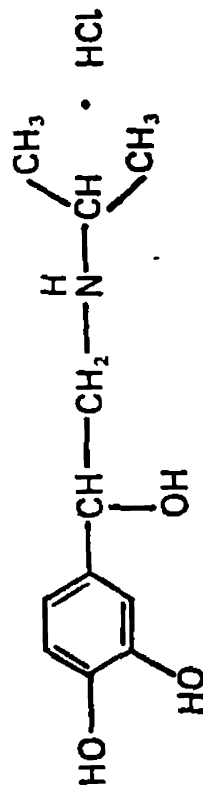
White crystalline powder, may have cream-coloured tint

13. Dibunol (*Dibunolum*)



White crystalline powder, may have slightly yellowish tint

14. Isadrin (isoprenaline, novodrin) (*Isadrinum*)



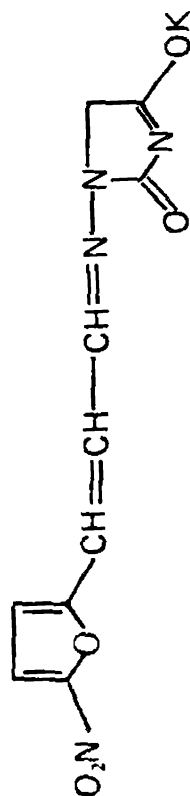
White crystalline powder

monium molybdate solution in concentrated sulphuric acid; a blue colour appears that rapidly vanishes (a secondary amino group); (3) a reaction with a silver nitrate solution for chlorides	pressure; used in glaucoma	mological forms (3% and 5% solutions)
(1) Heat several grains of the drug in a dry test tube on a burner flame, in some time crystals (dibunol) appear on the walls in the upper part of the tube; (2) to a solution of the drug in isopropanol add 2 ml of a solution of <i>o</i> -dianisidine hydrochloride and 1 ml of a 0.2% sodium nitrite solution, in some time agitate the mixture with chloroform, which acquires a pink colour	Cytostatic, burn-healing agent; antiphlogistic agent	10% liniment (cytostatic action); 5% liniment (burn-healing action)
(1) Add an alkali solution; an isadrin base precipitates; (2) add a 5% iron(III) chloride solution; a green colour appears (phenol hydroxyls)	Bronchodilator: relieves and prevents attacks of bronchial asthma; prescribed for emphysematous bronchitis and pneumosclerosis	0.5 and 1% solutions in 25- and 100-ml bottles; 0.005-g tablets

Name, structure, description	Identification *	Main use	Medical form
Aromatic amines and their derivatives			
15. Sulphapyridazine (<i>Sulfapyridazinum</i>) White odourless crystalline powder, may have slightly yellowish tint, with bitter taste	(1) Forms an azo dye (aromatic amino group); (2) forms salts having a characteristic colour with a copper sulphate solution (sulphamide group)	Antibacterial agent with prolonged action (pneumonia, bronchitis, tonsillitis, pharyngitis, dysentery)	0.5-g powders and tablets
16. Phthazin (<i>Phthazinum</i>) White odourless crystalline powder, may have slightly bitter taste	(1) After acid hydrolysis forms an azo dye (aromatic amino group); (2) fuse a few grains of the drug with resorcin and 2-3 drops of concentrated sulphuric acid, cool, and pour in a dilute alkali solution; bright green fluorescence is observed (phthalic acid residue)	Antibacterial agent with prolonged action; used to treat intestinal diseases: dysentery, enterocolitis, etc.	0.5-g powders and tablets
Heterocyclic compounds			
<i>Furan derivatives</i>			
17. Furazolidone (furaxone) (<i>Furazolidonum</i>)	(1) Add a 30% sodium hydroxide solution and heat; a brown colour appears; (2) a solution of the drug in dimethylformamide has a yellow colour; when	Antibacterial and antiprotozoal agent. Effective against lamblasis and intestinal infections: dysentery, typhus abdomina-	0.05-g tablets

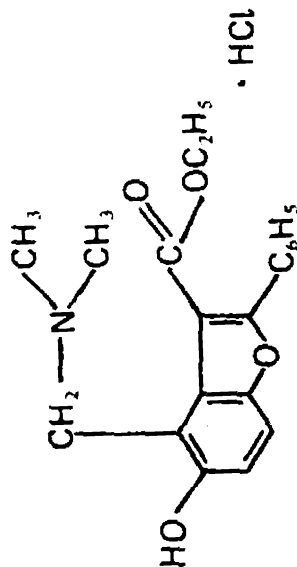
Yellow or greenish-yellow odourless powder, with slightly bitter taste

18. Furagin soluble (furazidin) (*Furaginum solubile*)



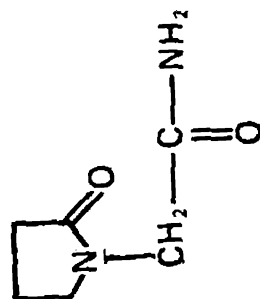
Red odourless powder with bitter taste, hygroscopic

19. Phenicaberan (*Phenicabaranum*)



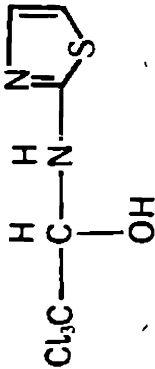
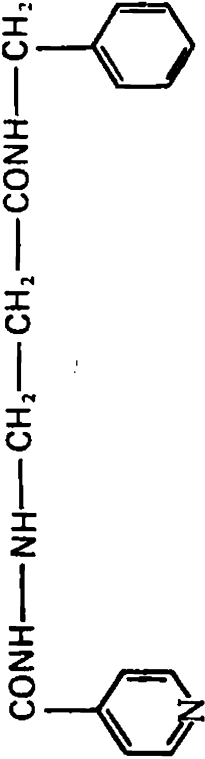
White or almost white crystalline powder

20. Piracetam (piracetam) (*Piracetamum*)

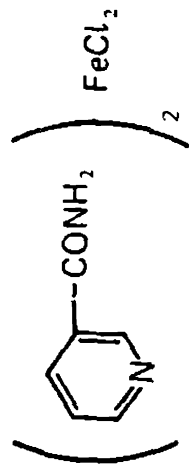


White crystalline powder

2 drops of a 1 N potassium hydroxide solution in 50% alcohol are added, a violet colour appears	lis, and paratyphoid	
Add a 30% sodium hydroxide solution and heat, a colour from yellow to brown appears	Antibacterial agent (sepsis, wound and purulent infections, pneumonia, inflammatory diseases of the urinary tracts)	Powder
(1) Add concentrated sulphuric acid, a yellow colour forms (benzofuran); (2) absorption peak of a 0.001% alkaline solution of the drug at a wavelength of 300 ± 3 nm; (3) a reaction with a silver nitrate solution for chlorides	Spasmodic agent	0.2-g coated tablets; 2-ml ampoules with 0.25% solution
<i>Pyrazolidine derivatives</i>		
(1) The ultraviolet spectrum of a 1% aqueous solution of the drug has no pronounced absorption peaks in the region from 230 to 350 nm; (2) heat with a small amount of an alkali solution: ammonia evolves that is detected by its odour and by a moist piece of litmus paper turning blue (amine)	Psychostimulating agent (actively affects various functions of the central nervous system)	0.4% solution for injections

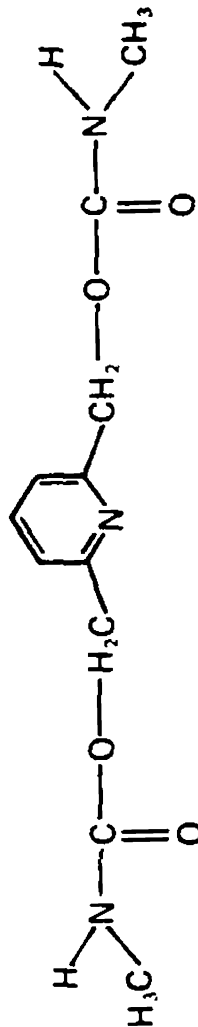
Name, structure, description	Identification *	Main use	Medical form
<i>Thiazole derivatives</i>			
21. Chlothazole (<i>Chlothasolum</i>)  Finely crystalline white powder, may have a creamish tint	(1) Heat in a test tube, bring filter paper wetted with a lead acetate solution up to the tube mouth, the paper turns brown (sulphide sulphur in the heterocyclic ring); (2) boil an alcohol solution of the drug for 2 min, cool, add a silver nitrate solution; a white precipitate forms that does not dissolve in nitric acid (chloride ion); (3) add 2 ml of a 2% sodium carbonate solution and 2 ml of a sodium hydroxide solution to 0.1 g of the drug, agitate up to dissolution, add 0.5 ml of a 1% sodium nitroprusside solution; a blue-violet colour is observed (secondary amine)	Antiphlogistic agent with analgesic and antipyretic action. Used to treat rheumatism	0.1-g tablets
<i>Pyridine and piperidine derivatives</i>			
22. Nialamide (nuredal) (<i>Nialamidum</i>)  White finely crystalline powder	Heat with Fehling's reagent; gas bubbles form (N ₂); next a red-orange copper(I) precipitate forms (hydrazine group)	Antidepressant—inhibitor of mono-aminooxidase (depressions, motor inhibition, asthenia)	0.025-g tablets (dragée)

23. Ferramide (*Ferramidum*)



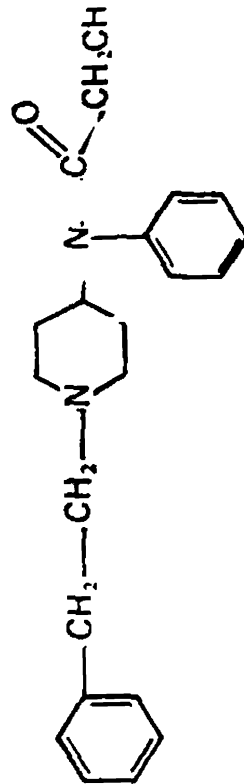
Yellow odourless crystalline powder with a metallic taste

24. Parmidine (pyridinol carbamate, anginin) (*Parmidinum*)



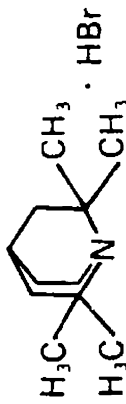
White or almost white crystalline powder

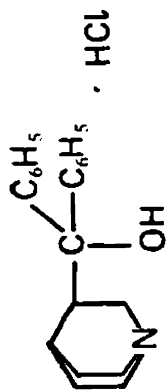
25. Fentanyl (phentanyl) (*Phentanylum*)



White crystalline powder

(1) Add several drops of hydrochloric acid and a solution of potassium hexacyanoferrate(III); a blue precipitate of Turnbull's blue forms (Fe^{2+}); (2) a reaction with a silver nitrate solution for chlorides; (3) heat with sodium carbonate; a smell of pyridine appears, and with an alkali solution—a smell of ammonia (a nicotinic acid amide)	Post-haemorrhagic and hypoferric anaemias of various origin	0.02- and 0.1-g tablets in glass bottles or jars
(1) Heat with an alkali solution; methylamine evolves that is detected by its odour and moist red litmus paper turning blue; (2) to 0.1 g of the drug add 0.05 g of citric acid, 1 ml of acetic anhydride, agitate, and heat in a water bath for 10 min; a yellow colour appears that gradually turns cherry-red (tertiary nitrogen)	Antisclerotic drug (cerebral, coronary, and peripheral atherosclerosis)	0.25-g tablets
(1) Dissolve 0.005 g of the drug in 2 ml of a 1% solution of citric acid in acetic anhydride and heat in a water bath; a red-violet colour appears (tertiary nitrogen);	Analgesic with short action (medicinal preparation for narcosis; lung and myocardial infarctions, nephritic colic, angina pectoris)	2- and 10-ml ampoules with 0.005% solution

Name, structure, description	Identification*	Main use	Medical form
	(2) mix 0.02 g of the drug with 0.04 g of citric acid, 10 ml of a buffer mixture (pH=5), 1 ml of a methyl orange solution, and 15 ml of chloroform in a separatory funnel; after stratification of the mixture, pour out 5 ml of the chloroform layer into a test tube, add 5 ml of a 1 N hydrochloric acid solution, and agitate the mixture; a reddish colour (piperidine) appears in the acid layer		
<i>Quinuclidine derivatives</i>			
26. Temechine (imequin, temequin) (<i>Temechinum</i>)  White crystalline powder, may have slightly creamish tint	Dissolve the drug in alcohol and slowly add an alcohol solution of cadmium iodide with stirring; a precipitate appears; after 40 min filter it, dry, and determine its melting point (254-258 °C); the decomposition temperature of temechine itself is 269-273 °C	Ganglion blocking agent, hypotensor (hypertension, spasms of peripheral vessels, gastric and duodenal ulcers)	0.001-g tablets 1-ml ampoules with 0.1% solution
27. Phencarol (<i>Phencarolum</i>)	(1) Add an ammonium reinekate solution and heat; a pink curdy precipitate	Antiallergic drug (acute and chronic urticaria, allergic	0.01-, 0.025-, and 0.05-g powders and tablets

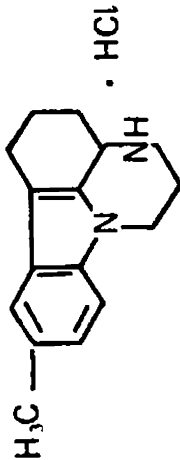


White odourless crystalline powder with bitter taste

rhinitis, dermatosis, eczema, skin itch, etc.)

itate forms that is soluble in acetone (quinuclidine);
 (2) add an alkali solution, agitate, and filter it; acidify the filtrate with nitric acid and add a silver nitrate solution; a white curdy precipitate forms (chlorides);
 (3) put several small crystals of the drug on an object glass and add three drops of a formaldehyde solution in concentrated sulphuric acid (Marchi's reagent); an intensive cherry-brown colour appears (aromatic rings)

28. Pyrazidole (*Pyrazidolum*)



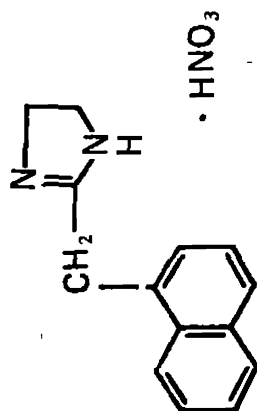
Light yellow crystalline powder with slightly greenish tint

Indole derivatives

(1) Add 1 ml of concentrated sulphuric acid and 0.01 g of sodium nitrate to 0.02 g of the drug; a yellow colour appears (pyrazidole); (2) the ultraviolet spectrum of an aqueous 0.005% solution in the region from 230 to 280 nm has an absorption peak at 233±2 nm; (3) a reaction with a silver nitrate solution for chlorides	Antidepressant (psychic diseases proceeding with depression)	0.025- and 0.05-g powders and tablets
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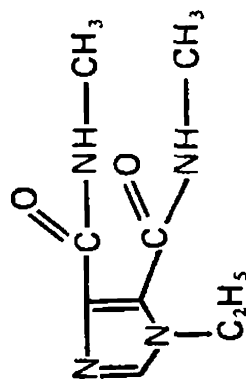
Name, structure, description	Identification*	Main use	Medical form
<i>Imidazole and imidazoline derivatives</i>			
29. Fentolamine (phentolamine) (<i>Phentolaminum</i>) White or slightly cream-coloured crystalline powder	Dissolve the drug in alcohol, add hydrochloric acid and an ammonium vanadate solution; a light green precipitate forms. Dissolve the drug in hot water and add a concentrated ammonia solution; an oily yellow liquid forms that freezes at room temperature (the phentolamine base)	Anti-adrenergic drug (disorders of peripheral blood circulation, trophic ulcers of extremities, bedsores, poorly healing wounds, frostbites)	0.025- g powders and tablets
30. Clofelin (clonidine, chlornidine, hemiton) (<i>Clophelinum</i>) White crystalline powder	(1) A reaction with a silver nitrate solution for chlorides; (2) the ultraviolet spectrum of a 0.02% solution in water in the region from 230 to 300 nm has two absorption peaks at 272 ± 2 nm and at 280 ± 2 nm; (3) the ultraviolet spectrum of an alkaline solution of the drug in the region from 235 to 280 nm has an absorption peak at 250 ± 2 nm (measured in comparison with an acidic clofelin solution)	Hypotensor (various forms of hypertension)	0.075- and 0.15-mg tablets; 1-ml ampoules with 0.01% solution

34. Naftizin (naphazoline, sanorin) (*Naphthyzinum*)



White crystalline powder, may have yellowish tint

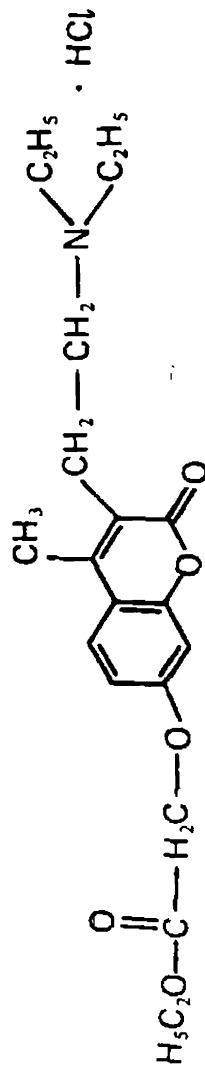
32. Ethimizole (*Aethimizolum*)



White crystalline powder

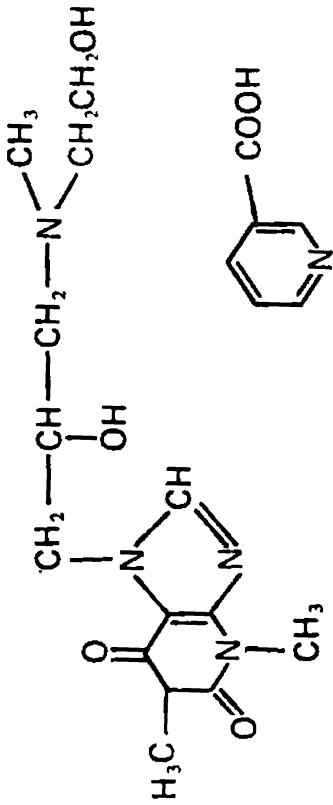
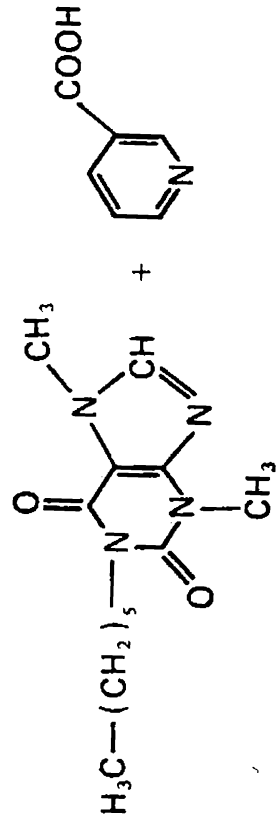
Chromone derivatives

33. Carbocromen (intensain, intercordin) (*Carbocromenum*)



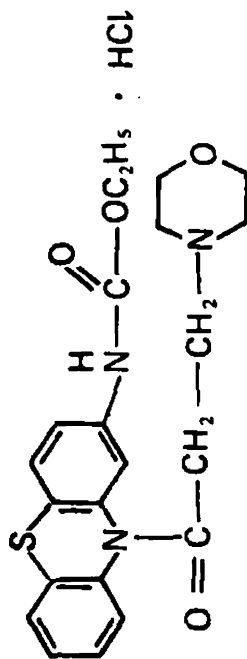
White finely crystalline powder with a light specific odour

Put an aqueous solution of the drug into a separatory funnel, add a sodium hydroxide solution, extract the naftizin base with ether and dry it; the melting point of the residue is 118-120 °C	An adrenomimetic drug: constricts the peripheral blood vessels and raises the blood pressure, dilates the pupils. Used to treat rhinitis, coryza, and other allergic diseases of the nasal cavity	Solution (0.05 and 0.1%) in 10-ml bottles
Boil 0.1 g of the drug with 5 ml of a 30% sodium hydroxide solution, you feel a smell of meth-ylamine whose vapour causes moist litmus paper to turn blue (secondary amine)	Stimulates the respiratory centre. Is used as a respiration stimulator in poisoning by narcotics and analgesics, during and after surgical narcosis	0.1-g powders and tablets; 3- and 5-ml ampoules with 1 and 1.5% solution
(1) Heat with a potassium permanganate solution acidified with sulphuric acid, the pink solution loses its colour (an unsaturated carbon bond); (2) add a solution of an alkali and 4-aminophenol in 95% alcohol; the solution acquires a blue colour which becomes deeper when left standing (a reaction for the lactone ring);	An antiangina drug (angina pectoris, coronary sclerosis, prophylaxis of myocardial infarction during postinfarction period)	0.075-g tablets

Name, structure, description	Identification*	Main use	Medical form
	(3) the ultraviolet spectrum of a 0.001% solution of the drug in 55% alcohol has an absorption peak at a wavelength of 322 nm; (4) a reaction with a silver nitrate solution for chlorides		
<i>Purine derivatives</i>			
34. Xantinol nicotinate (complamin) (<i>Xantinioli nicotinas</i>) 	(1) Reaction with 2,4-dinitrochlorobenzene (pyridine ring) (see Sec. 27.3); (2) aqueous extraction of the drug (at 70 °C) with a copper sulphate solution forms a blue precipitate (carboxyl group of nicotinic acid); (3) the murexide test for the purine ring	Spasmolytic agent and hypotensor. Dilates peripheral vessels and strengthens heart beat	0.15-g tablets (dragée); 2- and 10-ml ampoules with 15% solution
White crystalline powder 35. Nigeksin (<i>Nihexynum</i>) 	(1) The murexide test for the purine ring; (2) reaction with a copper sulphate solution (see Xantinol nicotinate); (3) reaction with 2,4-dinitrochlorobenzene (see Sec. 27.3)	Vasodilator, improves the supply of blood to the brain (atherosclerosis)	Tablets containing 0.25 g of hexyltheobromine and 0.05 g of nicotinic acid
White crystalline powder			

Phenothiazine derivatives

36. Etmozine (moracizine) (*Aetmozinum*)



White crystalline powder, may have cream-coloured tint. Fades in light

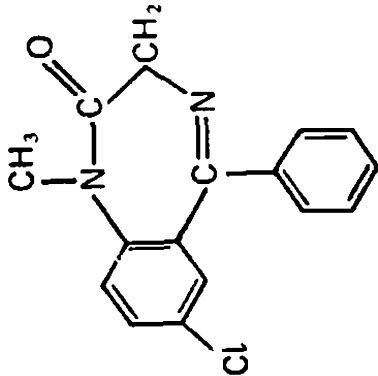
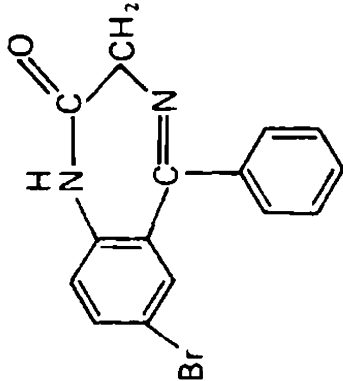
(1) Dissolve 0.05 g of the drug with heating in 6 ml of dilute hydrochloric acid, boil during 1 min; the solution gradually becomes turbid and a light lilac colour appears; cool the reaction mixture and divide it into two parts: dilute the first one with 7 ml of water and add 1 ml of bromine water, the colour becomes bright violet (phenothiazine derivative); filter the second part and add one drop of a sodium nitrite solution to the filtrate; a green colour appears that turns yellow; with time a yellow precipitate forms (morpholine); (2) heat 0.03 g of the drug with 1 ml of a sodium hydroxide solution and 2 drops of a 0.1 N iodine solution; you will feel an odour of iodoform (carboethoxy group); (3) precipitate the drug base with an alkali solution; determine chlorides in the filtrate with a silver nitrate solution

Coronary vessel dilatation, spasmolytic agent (arrhythmia due to overdose of cardiac glycosides)

0.025-g coated tablets; 2-ml ampoules with 2.5% solution

Appendix I (continued)

Name, structure, description	Identification*	Main use	Medical form
37. Nonachlazine (azachlorzine) (<i>Nonachlazinum</i>) <chem>ClC1=CC=C2C(=C1)N(C(=O)CCN3CCCC3)SC2.Cl</chem> Grayish yellow crystalline powder	(1) The ultraviolet spectrum of a 0.002% solution of the drug in a 0.1 <i>N</i> hydrochloric acid solution in the region of 250-300 nm has an absorption peak at 262 ± 2 nm; (2) heat with bromine water, a crimson colour appears (phenothiazine); (3) precipitate the nonachlazine base using an alkali solution; chlorides are detected in the filtrate by a reaction with a silver nitrate solution; (4) agitate an aqueous solution of the drug with bromophenol blue in the presence of benzene, a yellow colour appears [the distinction from the other drugs of the phenothiazine series except for ethapirazine (perphenazine) and meterazine (prochlorperazine)]	Spasmolytic and coronary vessel dilating agent (ischaemia, to prevent attacks; postinfarction angina pectoris)	0.03-g coated tablets
38. Ftoracizine (fluacizine) (<i>Phthoracizinum</i>)	Heat up to boiling with bromine water; the solution turns light crimson (phenothiazine)	Antidepressant with a sedative effect (troubled and depressed states)	0.04- and 0.025-g coated tablets; 1-ml ampoules with 1.25% so-

Name, structure, description	Identification*	Main use	Medical form
40. Sibazone (diazepam, seduxen) (<i>Sibazonum</i>) 	(1) Melt with an alkali; methylamine vapour evolves that colours red litmus paper blue (amine); (2) positive Beilstein's test for halogen (see Chlozepksid); (3) heat with 6 <i>N</i> hydrochloric acid, the solution turns yellow (aminobenzophenone)	Tranquilizer (close to chlozepksid, sometimes more effective, acts in smaller doses)	0.005-g tablets; 2-ml ampoules with 0.5% solution
Colourless crystals 41. Phenazepam (<i>Phenazepamum</i>) 	(1) Melt with an alkali, ammonia vapour evolves that colours moist red litmus paper blue (amine); (2) positive Beilstein's test for halogen (see Chlozepksid); (3) heat and boil with a 6 <i>N</i> hydrochloric acid solution, add sodium nitrite and 2-naphthol in an alkaline medium; a cherry red colour appears (primary amine after hydrolysis); (4) react a chloroform solution of the drug with perchloric, sulphuric, or hydrochloric acid; a green fluorescence appears that increases in ultraviolet light at a wavelength of 254 nm; (5) heat in a dry test tube on the flame of a burner, a violet melt forms.	Tranquilizer (neurotic states, insomnia)	0.005-g tablets and powders
Colourless crystals with reddish tint			

II. ANALYSIS OF DRUGS ACCORDING TO PRESCRIPTIONS

Analyse the following powder:

Phenobarbital, 0.05 g

Bromisoval, 0.15 g

Papaverine hydrochloride, 0.03 g

Caffeine and sodium benzoate, 0.025 g

Sodium tetraborate, 0.3 g

1. Write the prescription in Latin.

2. Perform identification reactions.

Phenobarbital. To 0.1 g of the powder add 0.5 ml of 95% alcohol, one or two drops of a cobalt nitrite solution, and one drop of an ammonia solution; a violet colour should appear.

Papaverine hydrochloride. (a) to 0.05 g of the powder add one or two drops of a formaldehyde solution in concentrated sulphuric acid and heat the mixture slightly in a water bath; a violet colour should appear;

(b) to 0.05 g of the powder add 0.5 ml of nitric acid and heat the mixture in a water bath; a yellow colour should appear.

Bromisoval. (a) to 0.03 g of the powder add 0.3 ml of water, 0.2 ml of concentrated sulphuric acid, and heat up to boiling; an odour of isovaleric acid should be felt;

(b) to 0.05 g of the powder add 0.5 g of perhydrol and 2 ml of concentrated sulphuric acid, in one or two minutes add 2 ml of water and after cooling the mixture agitate it with 2 ml of chloroform; the chloroform layer should be coloured yellow;

(c) to 0.05 g of the powder add four or five drops of Nessler's reagent and heat the mixture in a water bath; a yellow-orange precipitate should form.

Sodium tetraborate. Put 0.05 g of the powder into a porcelain bowl, add one to three drops of concentrated sulphuric acid, 2 ml of 95% alcohol, and ignite the mixture. The alcohol solution should burn with a flame having a green fringe.

Caffeine and sodium benzoate. To 0.1 g of the powder add 1 ml of water, 1 ml of dilute hydrochloric acid, 3 ml of ether, and agitate during one minute. After stratification, separate the ether layer, add 2 ml of water and 0.5 ml of 0.1 *N* sodium hydroxide to it and agitate the mixture. Next add one drop of an iron(III) chloride solution; a pink-yellow precipitate should form. Give a chemical substantiation of the above reactions.

3. Conduct a quantitative analysis.

Papaverine hydrochloride. Shake 0.1 g of the powder with 2 ml of water, next add three drops of a bromophenol blue solution diluted with acetic acid to a yellow-green colour (about 2 ml), and titrate with a 0.02 *N* silver nitrate solution until a violet colour appears (*a* ml). One millilitre of the 0.02 *N* silver nitrate solution corresponds to 0.007 517 g of papaverine hydrochloride.

Bromisoval and papaverine hydrochloride. To 0.05 g of the powder add 1 ml of a 10% sodium hydroxide solution and boil the mixture carefully for three or four minutes (direct the mouth of the test tube away from your face when boiling the mixture!). After cooling the mixture, add 2.5 ml of dilute nitric acid, six or seven drops of an ammonium iron alum solution, 2 ml of a 0.1 *N* silver nitrate solution, and agitate the mixture. Titrate the excess of the 0.1 *N* silver nitrate solution with a 0.1 *N* ammonium thiocyanide solution until a yellowish pink colour appears (*b* ml). Simultaneously perform a control test (*b*₁ ml). Calculate the amount of bromisoval from the difference between the volumes of the 0.1 *N* silver nitrate solution used in the titration of the sum (*b*₁ − *b*) ml and the volume of the 0.1 *N* silver nitrate solution (*a* ml) used in the titration of the papaverine hydrochloride divided by 10, i.e. [(*b*₁ − *b*) − *a*/(2 × 5)]. One millilitre of the 0.1 *N* silver nitrate solution corresponds to 0.022 31 g of bromisoval.

Notes: (1) a ml is divided by 5 because the concentration of the 0.2 N silver nitrate solution used for the titration of the papaverine hydrochloride is one-fifth of the concentration of the 0.1 N silver nitrate solution used for the titration of the sum of bromisoval and papaverine hydrochloride; (2) a ml is divided by 2 because the mass of the sample taken for determination of the papaverine hydrochloride is double that of the sample taken for determination of bromisoval together with papaverine hydrochloride.

Phenobarbital. Put 0.1 g of the powder into a dry test tube, add 2 ml of ether, and agitate the solution during one minute. After settling of the precipitate, filter the ether extracts into another test tube. Repeat the extraction of the phenobarbital with 2-ml portions of ether three or four times more, agitating one minute each time and filtering the ether extracts through the same filter. Add 2 ml of water and six or seven drops of a mixed indicator consisting of equal parts of phenolphthalein and thymol blue solutions to the ether extracts and titrate with a 0.02 N sodium hydroxide solution with agitation until the aqueous layer, after settling, becomes violet. One millilitre of the 0.02 N sodium hydroxide solution corresponds to 0.004 644 g of phenobarbital.

Sodium tetraborate. Dissolve the residues on the filter and in the test tube in 2 ml of water, add one drop of a methyl red solution, and titrate with a 0.1 N hydrochloric acid solution up to a pink colour. One millilitre of the 0.1 N hydrochloric acid solution corresponds to 0.019 07 g of sodium tetraborate.

Caffeine and sodium benzoate. Add 3 ml of ether and one drop of a methyl orange solution to the titrated liquid and titrate while stirring the mixture vigorously with a 0.02 N hydrochloric acid solution until the aqueous layer becomes pink after settling. One millilitre of the 0.02 N hydrochloric acid solution corresponds to 0.002 882 g of sodium benzoate.

Analyse the following mixture:

Ephedrine hydrochloride, 0.2 g
 Dimedrol (diphenhydramine), 0.05 g
 Novocaine (procaine), 0.05 g
 2% boric acid solution, 10 ml

1. Write the prescription in Latin.

2. Perform identification reactions.

Ephedrine hydrochloride. To 0.5 ml of the mixture add 8-10 drops of a 10% sodium hydroxide solution, two drops of a 10% copper sulphate solution, and agitate the mixture. A violet-blue colour should appear. Next add 2 ml of ether and again agitate the mixture. After settling, the ether layer should be coloured red-violet.

Dimedrol. Put four or five drops of the mixture into a porcelain bowl and evaporate until dry. Add two or three drops of concentrated sulphuric acid to the dry residue; a yellow colour should appear that should vanish when several drops of water are added.

Novocaine. To three-five drops of the mixture add five or six drops of dilute hydrochloric acid, two or three drops of a 1% sodium nitrite solution, and pour 0.1-0.3 ml of the mixture obtained into 1-2 ml of an alkaline solution of 2-naphthol; an orange-red precipitate should form. When 1-2 ml of 95% alcohol are added, the precipitate should dissolve with the appearance of a cherry red colour.

Boric acid. Evaporate three to five drops of the mixture in a porcelain bowl in a water bath until dry. Add 1 ml of alcohol to the residue and ignite it. The alcohol solution should burn with a flame having a green fringe. Give a chemical substantiation of the above reactions.

3. Conduct a quantitative analysis.

Novocaine. To 1 ml of the mixture add 2 ml of water, 1 ml of dilute hydrochloric acid, 0.2 g of potassium bromide, two drops of a tropeolin-00 solution, and a drop of a methylene blue solutions, and titrate at 18-20 °C with a 0.02 M

sodium nitrite solution, initially adding 0.2-0.3 ml every minute, and at the end of titration (from 0.1 to 0.2 ml before the equivalent point) one or two drops every minute until the red-violet colour turns blue (a ml). Simultaneously perform a control test (a_1 ml). One millilitre of a 0.02 M sodium nitrite solution corresponds to 0.005 456 g of novocaine.

Ephedrine hydrochloride, dimedrol, novocaine. To 1 ml of the mixture add two drops of a bromophenol blue solution and dilute acetic acid dropwise until a greenish yellow colour appears, and titrate with a 0.1 N silver nitrate solution up to a violet colour (b ml). Calculate the sum of the ephedrine hydrochloride and dimedrol from the difference between the volume of the 0.1 N silver nitrate solution (b) and that of the 0.02 M sodium nitrite solution ($a - a_1$) divided by 5, i.e. $[b - (a - a_1)/5]$. One millilitre of the 0.1 N silver nitrate solution corresponds to 0.021 97 g of the sum of ephedrine hydrochloride and dimedrol.

Novocaine, dimedrol, ephedrine hydrochloride and boric acid. To 0.5 ml of the mixture add 1 ml of water and a mixture consisting of 2 ml of chloroform, 2 ml of glycerin, and 1 ml of alcohol after neutralizing the mixture using phenolphthalein as an indicator. Titrate with a 0.1 N sodium hydroxide solution with agitation up to a pink colour of the aqueous layer. Add glycerin and continue the titration with the 0.1 N sodium hydroxide solution until a stable pink colour is obtained in the aqueous layer (c ml). Calculate the amount of boric acid from the difference between the volume of the 0.1 N sodium hydroxide solution (c) and that of the 0.1 N silver nitrate solution (b) divided by 2, i.e. $(c - b/2)$ ml. One millilitre of a 0.1 N sodium hydroxide solution corresponds to 0.006 183 g of boric acid.

Analyse the ointment "Sunoref" (Preobrazhensky's ointment):

Streptocid (sulphanilamide), 5 g
Norsulphazol (sulphathiazole), 5 g
Sulphadimezine (sulphadimidine), 5 g
Ephedrine hydrochloride, 1 g
Camphor, 0.3 g

Eucalyptus oil, 0.39 g
Vaseline (petroleum jelly), 100 g

1. Write the prescription in Latin.

2. Perform identification reactions.

Streptocid, norsulphazol, sulphadimezine.

(a) To 0.2 g of the ointment add 2 ml of dilute hydrochloric acid and heat until the vaseline melts. After cooling, separate the water extract and add two or three drops of a sodium nitrite solution. Pour 0.5 ml of the mixture into 1 ml of an alkaline solution of 1-naphthol, a cherry red colour should appear;

(b) to 0.5 g of the ointment add 3 ml of ether, 2 ml of a 0.1 N solution of sodium hydroxide and agitate the mixture. Next add two drops of a 10% copper sulphate solution; a yellow-green colour should appear that transforms into dirty violet.

Ephedrine hydrochloride. Put 0.5-0.7 g of the ointment into a test tube, add 2 ml of chloroform, 2 ml of water, and agitate until the vaseline dissolves. Separate the aqueous layer with a pipette and filter it through a filter wetted with water. To the aqueous filtrate add three drops of a 10% sodium hydroxide solution, one drop of a 10% copper sulphate solution, 3 ml of ether, 1 ml of alcohol, and agitate the mixture. The ether-alcohol layer after settling should be violet. Give a chemical substantiation of the above reactions.

3. Conduct a quantitative analysis.

Ephedrine hydrochloride. To 0.5 g of the ointment add 3 ml of ether, 1 ml of alcohol, 2 ml of water, and agitate until the vaseline and the drugs dissolve. Next add 0.5 ml of a 10% sodium hydroxide solution and again agitate for one minute. After settling, separate the ether layer with a pipette and filter it through

a filter together with 0.5 g of anhydrous sodium sulphate preliminarily wetted with ether. Repeat the extraction of the ephedrine base three or four times in 3-ml portions, each time agitating for one minute and add them to the first portion of the ether extract. Add 2 ml of water and one drop of a methyl orange solution to the ether extracts and titrate while shaking the mixture with a 0.02 *N* hydrochloric acid solution until the aqueous layer turns pink (*a* ml). Simultaneously run a control test. For this purpose, to a mixture of 9 ml of ether and 2 ml of water add one drop of a methyl orange solution and titrate with a 0.02 *N* hydrochloric acid solution until the aqueous layer turns pink (*a*₁ ml). Calculate the amount of ephedrine hydrochloride from the difference (*a* — *a*₁). One millilitre of 0.02 *N* hydrochloric acid corresponds to 0.004 034 g of ephedrine hydrochloride.

Norsulphazol, sulphadimezine, ephedrine hydrochloride. To 0.25 g of the ointment add a mixture of 2 ml of chloroform and 2 ml of alcohol neutralized using a mixed indicator consisting of equal parts of solutions of thymol blue and phenolphthalein, next add 2 ml of water and agitate until the base and the drugs dissolve. Titrate while agitating with a 0.1 *N* sodium hydroxide solution until the aqueous layer becomes violet (*b* ml). Use the difference between the volume of the 0.1 *N* sodium hydroxide solution (*b*) and the volume of the 0.02 *N* hydrochloric acid solution divided by 10, [*b* — (*a* — *a*₁)/(5 × 2)] to calculate the sum of the norsulphazol and sulphadimezine. One millilitre of the sodium hydroxide solution corresponds to 0.026 68 g of the sum of norsulphazol and sulphadimezine.

Notes: (1) We divide (*a* — *a*₁) ml by 5 because the concentration of the 0.1 *N* sodium hydroxide solution is five times greater than that of the 0.2 *N* hydrochloric acid solution; (2) we divide (*a* — *a*₁) ml by 2 because the mass of the ointment sample in determining the ephedrine hydrochloride is double that of the ointment when determining the norsulphazol and sulphadimezine.

Streptocid, norsulphazol, sulphadimezine. To 0.25 g of the ointment add 2 ml of chloroform, 2 ml of hydrochloric acid, and agitate the mixture until the base and drugs dissolve. Next add 2 ml of water, 0.2 g of potassium bromide, and two drops of a tropeolin-00 solution. Titrate with a 0.1 *M* sodium nitrite solution, first adding it at a rate of 0.2-0.3 ml a minute, and at the end of titration (0.1-0.2 ml before the equivalent amount) at a rate of one or two drops a minute until the red colour turns yellow (*c* ml).

Calculate the streptocid content in grammes by the formula

$$X = \frac{[(c - b) - (a - a_1)/(5 \times 2)] \times 0.0172 \times 116.7}{0.25}$$

where *c* is the amount of the 0.1 *M* sodium nitrite solution used to titrate the sum of the streptocid, norsulphazol, and sulphadimezine, ml, and [(*c* — *b*) — (*a* — *a*₁)/(5 × 2)] is the amount of the 0.1 *M* sodium nitrite solution used to titrate the streptocid. One millilitre of the 0.1 *M* sodium nitrite solution corresponds to 0.0172 g of streptocid.

Note: To calculate the content of ephedrine hydrochloride, the sum of norsulphazol and sulphadimezine, and also of streptocid, take three samples of the ointment with a mass of 0.5, 0.25, and 0.25 g, respectively. Other masses of the ointment samples will make the calculations more complicated.

Analyse the mixture:

Dimedrol (diphenhydramine), 0.05 g

Ephedrine hydrochloride, 0.4 g

Boric acid, 0.2 g

Furacilin (nitrofurazone), 0.002 g

0.8% streptocid (sulphanilamide) solution, 20 ml

1. Write the prescription in Latin.

2. Perform identification reactions.

Streptocid. (a) Put two or three drops of the mixture on a strip of newspaper and add one or two drops of dilute hydrochloric or sulphuric acid. An orange colour should appear on the paper.

(b) To three-five drops of the mixture add three-five drops of a 3% hydrogen peroxide solution and the same amount of an iron(III) chloride solution. A red colour should appear that gradually turns brown.

Dimedrol. To three-five drops of the mixture add one drop of dilute hydrochloric acid, two drops each of a 10% copper sulphate solution and a 5% ammonium thiocyanide solution. A brown colour should appear.

Ephedrine hydrochloride. To 0.5 ml of the mixture add 8-10 drops of a 10% sodium hydroxide solution, two drops of a 10% copper sulphate solution, 2 ml of ether, and agitate the mixture; after settling, the ether layer should be coloured red-violet.

Boric acid. Evaporate three-five drops of the mixture in a porcelain bowl in a water bath until dry. Add 1 ml of alcohol to the residue and ignite it. The alcohol solution should burn with a flame having a green fringe.

Furacilin. To 0.5 ml of the mixture add five drops of a 10% sodium hydroxide solution; a white precipitate should form (dimedrol, ephedrine) and a red-orange colour should appear (furacilin). Give a chemical substantiation of the above reactions.

3. Conduct a quantitative analysis.

Streptocid. To 0.5 ml of the mixture add 1 ml of dilute hydrochloric acid, 2 ml of water, 0.1 g of sodium bromide, two drops of a tropeolin-00 solution, one drop of a methylene blue solution, and titrate with a 0.02 *M* sodium nitrite solution, initially adding 0.2-0.3 ml a minute, and at the end of titration (0.1-0.2 ml before the equivalent point) one or two drops a minute until the red-violet colour turns green. One millilitre of the 0.02 *M* sodium nitrite solution corresponds to 0.003 444 g of streptocid.

Dimedrol, ephedrine hydrochloride. To 1 ml of the mixture add five drops of a 10% sodium hydroxide solution, 1 ml of alcohol, 2 ml of ether, and agitate the mixture for one minute. After settling, transfer the ether layer with a pipette onto a filter containing 1 g of anhydrous sodium sulphate and filter the mixture into a different test tube. Repeat the extraction with ether in 2-ml portions three more times, agitating each time for one minute and filtering through the same filter. At the end of the extractions, rinse the filter with 2 ml of ether. Add 2 ml of water to the ether extracts, one drop of a methyl orange solution, and titrate with agitation with a 0.1 *N* hydrochloric acid solution up to an orange-pink colour of the aqueous layer (*a* ml). One millilitre of the 0.1 *N* hydrochloric acid solution corresponds to 0.02 117 g of the sum of dimedrol and ephedrine hydrochloride.

Boric acid, dimedrol, ephedrine hydrochloride. To 0.5 ml of the mixture add 2 ml of chloroform, 1 ml of alcohol, 2 ml of glycerin neutralized using phenolphthalein as an indicator, and titrate while agitating with a 0.1 *N* sodium hydroxide solution until the aqueous layer after settling becomes pink. Next add 2 ml more of the neutralized glycerin and if the colour disappears, titrate once more until a pink colour appears. Continue to add glycerin and titrate with the 0.1 *N* sodium hydroxide solution until the pink colour stops disappearing (*b* ml).

Calculate the amount of boric acid from the difference between the volume of the 0.1 *N* sodium hydroxide solution (*b*) and that of the 0.1 *N* hydrochloric acid solution (*a*) divided by two ($b - a/2$) ml. One millilitre of the 0.1 *N* sodium hydroxide solution corresponds to 0.006 183 g of boric acid.

Analyse the mixture:

Boric acid, 0.2 g

Resorcin (resorcinol), 0.1 g

0.25% Zinc sulphate solution, 10 ml

1. Write the prescription in Latin.

2. Perform identification reactions.

Zinc ion. To two or three drops of the mixture add two or three drops of a potassium hexacyanoferrate(II) solution. A white curdy precipitate should form that does not dissolve in dilute hydrochloric acid.

Sulphate ion. To three-five drops of the mixture add two or three drops of a barium chloride solution. A white precipitate insoluble in diluted acids should form.

Boric acid. Evaporate three-five drops of the mixture in a porcelain bowl in a water bath until dry. Add 0.5 ml of 95% alcohol to the residue and ignite it. The solution should burn with a flame having a green fringe.

Resorcin. To four or five drops of the mixture add one drop of an iron(III) chloride solution. A violet colour should appear that turns brownish yellow when a few drops of an ammonia solution are added.

3. Conduct a quantitative analysis.

Zinc sulphate. To 1 ml of the mixture add 2 ml of an ammonia buffer solution, 0.02 g of the indicator Acid Chrom Black Special and titrate with a 0.01 M Na-EDTA solution until a blue colour appears. One millilitre of the 0.01 M Na-EDTA solution corresponds to 0.002 876 g of zinc sulphate.

Boric acid. To 0.5 ml of the mixture add 8-12 drops of a potassium hexacyanoferrate(III) solution, and 2 ml of glycerin neutralized with a 0.1 N sodium hydroxide solution using phenolphthalein as an indicator. Titrate while agitating with the 0.1 N sodium hydroxide solution until a pink colour appears. Next add another 2 ml of the neutralized glycerin and if the colour disappears, continue titration with the 0.1 N sodium hydroxide solution until the pink colour stops disappearing after the neutralized glycerin is added. One millilitre of the 0.1 N sodium hydroxide solution corresponds to 0.006 183 g of boric acid.

Resorcin. Put 1 ml of the mixture into a 10-ml measuring cylinder and bring the volume of the solution up to the mark by adding water (solution A). Put 2 ml of solution A into a test tube with a stopper, add 2 ml of a 0.1 N potassium bromate solution, 0.05 g of potassium iodide, 2 ml of dilute sulphuric acid, mix the ingredients, and let the mixture stand in a dark spot for five minutes. Next add 0.2 g of potassium iodide and 2 ml of chloroform to the mixture, and titrate the evolved iodine with a 0.1 N sodium thiosulphate solution with agitation until the colour vanishes.

Simultaneously perform a control test. One millilitre of the 0.1 N potassium bromate solution corresponds to 0.001 835 g of resorcin.

4. Compile the formulas needed for calculations and evaluate the required quantities.

5. Write the equations of the chemical reactions.

Analyse the mixture:

Riboflavin, 0.002 g

Thiamine bromide, 0.03 g

Ascorbic acid, 0.02 g

Potassium iodide, 0.2 g

Boric acid, 0.2 g

2% glucose solution, 10 ml

1. Write the prescription in Latin.

2. Perform identification reactions.

Ascorbic acid. To one or two drops of the mixture add one drop each of a solution of potassium hexacyanoferrate(III) and iron(III) chloride. A blue colour should appear.

Iodide ion. To four or five drops of the mixture add one or two drops of a lead acetate solution. A yellow colour should appear.

Boric acid. Evaporate three-five drops of the mixture in a bowl in a water

bath until dry. Add 0.5 ml of alcohol to the residue and ignite it. The alcohol solution should burn with a flame having a green fringe.

Glucose. (a) To one or two drops of the mixture add 0.01 g of thymol, and five or six drops of concentrated sulphuric acid. A red colour should appear that becomes stronger with slight heating;

(b) to one or two drops of the mixture add 0.5 ml of Fehling's reagent and heat the mixture; a red-orange precipitate should form.

Thiamine bromide. Determine it according to its specific odour.

Riboflavin. Detect it according to the characteristic yellow-green colour of the solution with a yellow fluorescence in the near-wall and surface layers.

3. Conduct a quantitative analysis.

Ascorbic acid. To 2 ml of the mixture add six or seven drops of a starch solution and titrate with a 0.1 *N* iodine solution until a blue colour appears (*b* ml). One millilitre of the 0.1 *N* iodine solution corresponds to 0.088 06 g of ascorbic acid.

Potassium iodide. To 0.5 ml of the mixture add four drops of dilute sulphuric acid and 0.04 g of urea. Next add slowly, dropwise, 1 ml of a 0.1 *M* sodium nitrite solution with agitation. Agitate the reaction mixture for seven or eight minutes up to complete evolution of the nitrogen oxides. Next add 0.1 g of potassium iodide to dissolve the evolving iodine, and titrate with a 0.1 *N* sodium thiosulphate solution until the colour disappears (at the end of titration add two or three drops of a starch solution) (*d* ml).

Simultaneously run a control test (*d*₁ ml). One millilitre of a 0.1 *N* sodium thiosulphate solution corresponds to 0.0166 g of potassium iodide. Compile the formulas for the calculations and evaluate the required quantities.

Ascorbic acid, boric acid, thiamine bromide. To 0.5 ml of the mixture add 2-3 ml of glycerin preliminarily neutralized using phenolphthalein as an indicator, and titrate with a 0.1 *N* sodium hydroxide solution up to an orange-pink colour. Next add another 2-3 ml of neutralized glycerin to the solution, and if the orange-pink colour disappears, continue titration until the solution acquires an orange-pink colour (*a* ml). Determine the sum of potassium iodide and thiamine bromide in the titrated liquid.

Potassium iodide and thiamine bromide. To the titrated liquid add 1 ml of dilute nitric acid, six or seven drops of a solution of iron(III) ammonium sulphate, 0.2 ml of a 0.02 *N* ammonium thiocyanide solution (*f* ml), and titrate with a 0.02 *N* silver nitrate solution until the orange colour turns yellow (*c* ml).

Calculate the sum of the thiamine bromide and potassium iodide from the difference between the volume of the 0.02 *N* silver nitrate solution (*c*) and 0.2 ml (*f*), i.e. the volume of the ammonium thiocyanide solution (*c* — *f*). Calculate the amount of thiamine bromide from the difference between the volume of the 0.02 *N* silver nitrate solution used for the sum of the thiamine bromide and potassium iodide, and the volume of the 0.02 *N* sodium thiosulphate solution used to titrate the potassium iodide:

$$e = (c - f) - (d - a) \times 5 \text{ ml.}$$

One millilitre of the 0.02 *N* silver nitrate solution corresponds to 0.004 352 g of thiamine bromide.

Note: We multiply (*d* — *a*) ml by 5 because the concentration of the 0.1 *N* sodium thiosulphate solution is higher than that of the 0.02 *N* silver nitrate solution five times.

4. Calculate the content of boric acid in grammes by the following formula

$$X = \frac{[a - b / (2 \times 2) - e \times 2 / 5] \times 0.006\ 183 \times 10}{0.5}$$

where a is the volume of the 0.1 N sodium hydroxide solution used for the titration of the sum of ascorbic and boric acids and thiamine bromide, ml, and $b/(2 \times 2)$ is the volume of the 0.1 N sodium hydroxide solution used for titration of the ascorbic acid, ml.

Notes: (a) b ml is divided by 2 because the mass of the sample used in determining the ascorbic acid is double that used in determining the sum of the ascorbic and boric acids and thiamine bromide, and $e \times 2/5$ is the volume of the 0.1 N sodium hydroxide solution used to titrate the thiamine bromide, ml;

(b) e ml is divided by 5 because the concentration of the 0.02 N silver nitrate solution is five times lower than that of the 0.1 N sodium hydroxide solution; e ml is multiplied by 2 because the volume of the 0.1 N sodium hydroxide solution used for the titration of the thiamine bromide is half the volume of the 0.1 N silver nitrate solution. One millilitre of the 0.1 N sodium hydroxide solution corresponds to 0.006 183 g of boric acid.

Glucose. Use a refractometer to determine the refractive index of the analyte solution and then the quantitative content of glucose in per cent by the formula

$$X = \frac{(n - n_0) - (F_1 C_1 + F_2 C_2 + F_3 C_3 + F_4 C_4) \times 100}{F \times 100}$$

where n is the refractive index of the analyte solution, n_0 is the same of water (1.333), F , F_1 , F_2 , F_3 , F_4 are refractive index growth factors for the solutions of glucose ($F = 0.001\ 42$), ascorbic acid ($F_1 = 0.0016$), thiamine bromide ($F_2 = 0.002$), potassium iodide ($F_3 = 0.0013$), and boric acid ($F_4 = 0.00063$), respectively, C_1 , C_2 , C_3 , C_4 are the concentrations of the solutions of ascorbic acid, thiamine bromide, potassium iodide, and boric acid, respectively, found by a chemical procedure and expressed in per cent.

5. Write the equations of the chemical reactions.

6. Conclude whether the eye drops may be dispensed.

The analysis should be performed during six hours.

The prescription is chosen and the time for analysis of the mixture is determined by the instructor.

III. REFRACTOMETRIC TABLES

TABLE IIIA. Refractive Indices and Refractive Index Factors* of Solutions with Various Weight-Volume Concentrations

Con- centra- tion, %	Amidopyrine (aminophenazone)		Anhydrous glucose**		Potassium iodide		Amfnoapric acid		Ascorbic acid		Boric acid	
	n_D^{20}	F^{***}	n_D^{20}	F	n_D^{20}	F	n_D^{20}	F	n_D^{20}	F	n_D^{20}	F
1	1.3353	For all concen- trations 0.00225	1.3344	For all concen- trations 0.00142	1.3343	For all concen- trations 0.00130	1.3349	For all concen- trations 0.00185	1.3346	0.00160	1.3337	For all concen- trations 0.00067
2	1.3375		1.3358		1.3356		1.3367		1.3362		1.3343	
3	1.3398		1.3373		1.3369		1.3386		1.3378		1.3350	
4	1.3420		1.3387		1.3382		1.3404		1.3394		1.3357	
5	1.3442		1.3401		1.3395		1.3423		1.3409			
6			1.3415		1.3408		1.3441		1.3425			
7			1.3429		1.3421		1.3460		1.3441			
8			1.3444		1.3434		1.3478		1.3456			
9			1.3458		1.3447				1.3471			
10			1.3472		1.3460				1.3487			
15			1.3543		1.3525							
20			1.3614		1.3590							
25			1.3685									
30			1.3756									
40			1.3898									

* The refractive indices are generally determined with an accuracy to the fourth digit after the decimal point, while the refractive index factors are given with five significant digits. The discrepancies here are insignificant and do not substantially affect the results of analysis.
** For the final calculation of the concentration of glucose solutions intended for oral use, add 10% to the sum of the per cent for glucose (to take moisture into account).
*** The factor F is the growth (increment) in the refractive index when the concentration increases by 1%. The concentration x of the analyte solution after finding the refractive index n is determined by the formula $x = (n - n_0)/F$, where n_0 is the refractive index of the solvent at the same temperature.

TABLE IIIA (concluded)

Con- centra- tion, %	Analgin·H ₂ O (novaminsulphon)		Barbital sodium		Hexamethylene- tetramine (methena- mine)		Magnesium sulphate		Sodium benzoate		Sodium bromide	
	²⁰ _{<i>n</i>_D}	<i>F</i>	²⁰ _{<i>n</i>_D}	<i>F</i>	²⁰ _{<i>n</i>_D}	<i>F</i>	²⁰ _{<i>n</i>_D}	<i>F</i>	²⁰ _{<i>n</i>_D}	<i>F</i>	²⁰ _{<i>n</i>_D}	<i>F</i>
1	1.3349	0.00194	1.3348	For all	1.3347	0.00167	1.3340	0.00096	1.3352	0.00217	1.3343	0.00134
5	1.3427	0.00194	1.3421	concen- trations	1.3414	0.00168	1.3377	0.00095	1.3438	0.00216	1.3397	0.00133
10	1.3523	0.00193	1.3512	0.00182	1.3498	0.00168	1.3423	0.00093	1.3544	0.00214	1.3462	0.00132
15	1.3620	0.00193	1.3603		1.3584	0.00169	1.3468	0.00092	1.3649	0.00213	1.3526	0.00131
20	1.3714	0.00192			1.3670	0.00170	1.3511	0.00090	1.3753	0.00211	1.3590	0.00130
25	1.3810	0.00192			1.3656	0.00170	1.3553	0.00089				
30	1.3903	0.00191			1.3843	0.00171	1.3594	0.00088				
40	1.4090	0.00190			1.4019	0.00172	1.3670	0.00085				
50	1.4275	0.00189					1.3740	0.00082				

Con- centra- tion, %	Potassium bromide		Calcium chloride		Caffeine and sodium benzoate		Sodium iodide		Sodium salicylate		Sodium chloride	
	²⁰ _{<i>n</i>_D}	<i>F</i>	²⁰ _{<i>n</i>_D}	<i>F</i>	²⁰ _{<i>n</i>_D}	<i>F</i>	²⁰ _{<i>n</i>_D}	<i>F</i>	²⁰ _{<i>n</i>_D}	<i>F</i>	²⁰ _{<i>n</i>_D}	<i>F</i>
1	1.3342	0.00120	1.3342	0.00118	1.3349	For all	1.3344	For all	1.3350	0.00201	1.3347	0.00170
5	1.3390	0.00119	1.3489	0.00117	1.3426	concen- trations	1.3402	concen- trations	1.3431	0.00201	1.3413	0.00167
10	1.3448	0.00118	1.3446	0.00116	1.3522	0.00192	1.3473	0.00143	1.3530	0.00200	1.3493	0.00164
15	1.3505	0.00117	1.3503	0.00115	1.3618		1.3545		1.3629	0.00199	1.3570	0.00160
20	1.3562	0.00116	1.3558	0.00114	1.3714		1.3616		1.3726	0.00198	1.3644	0.00157
25			1.3613	0.00113								
30			1.3666	0.00112								
40			1.3770	0.00110								
50			1.3870	0.00108								

TABLE IIIB. Refractive Indices of Solutions for Various Weight-Volume Concentrations

Refractive index n_D^{20}	Concentration of solutions, %					
	Potassium iodide	Potassium chloride	Calcium chloride	Ascorbic acid	Codeine phosphate	Caffeine and sodium ben- zoate
1.3340	0.75	0.77	0.85	0.62	0.55	0.60
1.3350	1.53	1.54	1.71	1.24	1.15	1.20
1.3360	2.30	2.31	2.56	1.88	1.70	1.70
1.3370	3.05	3.08	3.42	2.52	2.25	2.20
1.3380	3.80	3.85	4.28	3.16	2.80	2.70
1.3390	4.58	4.67	5.15	3.80	3.35	3.20
1.3400	5.35	5.46	6.00	4.44	3.90	3.70
1.3410	6.10	6.24	6.90	5.03	4.45	4.20
1.3420	6.85	7.04	7.79	5.72	5.00	4.70
1.3430	7.60	7.84	8.65	6.36	5.55	5.20
1.3440	8.40	8.64	9.50	7.00	6.10	5.70
1.3450	9.15	9.44	10.40	7.64	6.65	6.20
1.3460	9.93	10.24	11.20	8.28	7.20	6.70
1.3470	10.70	11.05	12.10	8.92	7.75	7.20
1.3480	11.75	11.87	13.00	9.56	8.30	7.70
1.3490	12.25	12.68	13.90	10.20	8.85	8.20
1.3500	13.00	13.50	14.78		9.40	8.70
1.3510	13.78	14.32	15.67		10.00	9.20
1.3520	14.55	15.14	16.57		10.55	9.70
1.3530	15.35	15.97	17.47		11.10	10.20
1.3540	16.13		18.36			10.70
1.3550	16.88		19.28			11.20
1.3560	17.65		20.19			11.70
1.3570	18.43		21.09			12.20
1.3580	19.20		22.00			12.70
1.3590	20.00		22.91			13.20
1.3600	20.75		23.81			13.70
1.3610			24.78			14.20
1.3620			25.78			14.70
1.3630			26.69			15.20
1.3640			27.62			
1.3650			28.55			
1.3660			29.45			
1.3670			30.35			
1.3680			31.25			
1.3690			32.19			
1.3700			33.15			
1.3710			34.15			
1.3720			35.10			
1.3730			36.10			
1.3740			37.10			
1.3750			38.05			
1.3760			39.00			
1.3770			39.95			
1.3780			40.90			
1.3790			41.85			
1.3800			42.80			
1.3810			43.80			
1.3820			44.80			
1.3830			45.80			
1.3840			46.80			

TABLE IIIB (continued)

Refractive index n_D^{20}	Concentration of solutions, %					
	Potassium iodide	Potassium chloride	Calcium chloride	Ascorbic acid	Codeine phosphate	Caffeine and sodium ben- zoate
1.3850			47.75			
1.3860			48.75			
1.3870			49.80			
1.3880			50.85			
1.3890			51.85			
1.3900			52.90			
1.3910			53.85			
1.3920			55.00			
1.3930			56.05			
1.3940			57.07			
1.3950			58.10			
1.3960			59.10			
1.3970			60.10			
1.3980			61.13			

Refractive index n_D^{20}	Concentration of solutions, %					
	Magnesi- um sul- phate	Copper sulphate	Sodium benzoate	Sodium bromide	Sodium hy- drogen carbo- nate	Sodium iodide
1.3340	1.05	0.91	0.45	0.75	0.80	0.71
1.3350	2.09	1.68	0.92	1.50	1.60	1.41
1.3360	3.10	2.61	1.39	2.26	2.40	2.10
1.3370	4.13	3.51	1.86	3.00	3.20	2.80
1.3380	5.15	4.39	2.35	3.74	4.00	3.49
1.3390	6.20	5.31	2.81	4.50	4.80	4.20
1.3400	7.35	6.19	3.26	5.24	5.60	4.80
1.3410	8.45	7.14	3.72	6.00	6.40	5.58
1.3420	9.65	8.04	4.18	6.76	7.20	6.27
1.3430	10.75	8.89	4.63	7.54	8.00	6.96
1.3440	11.80	9.82	5.07	8.32	8.80	7.65
1.3450	12.95	10.71	5.53	9.06	9.60	8.35
1.3460	14.05	11.61	6.00	9.81	10.40	9.04
1.3470	15.22	12.50	6.48	10.57		9.74
1.3480	16.34	13.40	6.95	11.32		10.44
1.3490	17.50	14.30	7.41	12.09		11.15
1.3500	18.70		7.88	12.88		11.85
1.3510	19.90		8.35	13.67		12.55
1.3520	21.10		8.83	14.46		13.26
1.3530	22.10		9.30	15.25		13.97
1.3540	23.45		9.77	16.03		14.67
1.3550	24.70		10.24	16.81		15.37
1.3560	25.85		10.71	17.60		16.05
1.3570	27.10		11.19	18.38		16.75
1.3580	28.40		11.66	19.16		17.45
1.3590	29.50		12.14	19.96		18.15
1.3600	30.75		12.63	20.77		18.85
1.3610	32.00		13.10	21.55		19.58

TABLE IIIB (continued)

Refractive index n_D^{20}	Concentration of solutions, %					
	Magnesi- um sul- phate	Copper sulphate	Sodium benzoate	Sodium bromide	Sodium hy- drogen carbo- nate	Sodium iodide
1.3620	33.35		13.58	22.35		20.28
1.3630	34.66		14.06	23.15		
1.3640	35.90		14.53	23.96		
1.3650	37.24		15.01	24.76		
1.3660	38.60		15.50	25.42		
1.3670	39.90		15.98			
1.3680	41.25		16.47			
1.3690	42.63		16.95			
1.3700	43.95		17.42			
1.3710	45.30		17.92			
1.3720	46.64		18.43			
1.3730	47.96		18.91			
1.3740	49.34		19.40			
1.3750	50.70		19.88			
1.3760	52.00		20.37			
1.3770			20.86			
1.3780			21.35			
1.3790			21.85			
1.3800			22.34			
1.3810			22.83			
1.3820			23.32			
1.3830			23.82			
1.3840			24.32			
1.3850			24.84			
1.3860			25.35			

Refractive index n_D^{20}	Concentration of solutions, %					
	Sodium nor- sulphazole (sulphathia- zole)	Sergosin (methio- dal sodium)	Sulphacyl (sulphaceta- mide) sodium	Formalde- hyde	Chloral hydrate	Ephedrine hydro- chloride
1.3340	0.55	1.05	0.50	0.92	0.99	0.50
1.3350	1.14	2.10	1.00	1.83	1.80	1.00
1.3360	1.70	3.10	1.60	2.74	2.65	1.50
1.3370	2.29	4.15	2.10	3.64	3.50	2.00
1.3380	2.87	5.15	2.60	4.54	4.35	2.50
1.3390	3.41	6.15	3.10	5.44	5.25	3.00
1.3400	4.01	7.20	3.60	6.34	6.15	3.50
1.3410	4.58	8.25	4.10	7.23	7.00	4.00
1.3420	5.16	9.25	4.60	8.12	7.90	4.50
1.3430	5.71	10.30	5.10	9.01	8.80	5.00
1.3440	6.36	11.30	5.60	9.91	9.70	5.50
1.3450	6.87	12.30	6.10	10.80	10.60	6.00
1.3460	7.45	13.35	6.60	11.68	11.50	6.50
1.3470	8.00	14.40	7.10	12.55	12.40	7.00
1.3480	8.55	15.45	7.60	13.43	13.30	7.50
1.3490	9.23	16.50	8.10	14.30	14.15	8.00
1.3500	9.77	17.50	8.60	15.17	15.00	8.50
1.3510	10.33	18.50	9.10	16.05	15.90	9.00

TABLE IIIB (concluded)

Refractive index n_D^{20}	Concentration of solutions, %s					
	Sodium nor- sulphazole (sulphathia- zole)	Sergosin (methio- dal sodium)	Sulphacyl (sulphaceta- mide) sodium	Formalde- hyde	Chloral hydrate	Ephedrine hydro- chloride
1.3520		19.50	9.60	16.90	16.80	9.50
1.3530		20.55	10.10	17.77	17.70	10.00
1.3540		21.60	10.60	18.63	18.60	10.50
1.3550		22.65	11.10	19.49	19.50	
1.3560		23.70	11.60	20.34	20.40	
1.3570		24.70	12.10	21.19	21.30	
1.3580		25.75	12.60	22.05	22.20	
1.3590		26.80	13.10	22.90	23.10	
1.3600		27.85	13.60	23.74	24.00	
1.3610		28.90	14.10	24.58	24.85	
1.3620		30.00	14.60	25.41	25.75	
1.3630		31.00	15.10	26.26	26.60	
1.3640		32.00	15.60	27.09	27.60	
1.3650		33.00	16.10	27.93	28.40	
1.3660		34.20	16.60	28.76	29.30	
1.3670		35.20	17.10	29.58	30.20	
1.3680		36.20	17.60		30.45	
1.3690		37.30	18.10		31.24	
1.3700		38.30	18.60		32.08	
1.3710		39.40	19.10		32.90	
1.3720		40.50	19.60		33.70	
1.3730		41.50	20.10		34.50	
1.3740		42.50	20.60		35.30	
1.3750		43.50	21.10		36.10	
1.3760		44.50	21.60		36.92	
1.3770		45.70	22.10		37.75	
1.3780		46.80	22.60		38.55	
1.3790		47.80	23.10		39.36	
1.3800		48.90	23.60		40.16	
1.3810		50.00	24.10			
1.3820		51.00	24.60			
1.3830		52.00	25.10			
1.3840			25.60			
1.3850			26.10			
1.3860			26.60			
1.3870			27.10			
1.3880			27.60			
1.3890			28.10			
1.3900			28.60			
1.3910			29.10			
1.3920			29.60			
1.3930			30.10			
1.3940			30.60			
1.3950			31.10			
1.3960			31.60			
1.3970			32.10			
1.3980			32.60			
1.3990			33.10			

Note. To find the content of formalin in a solution in per cent, multiply the content of formaldehyde found in the table by the factor 2.7. The latter has been determined with a view to the average (37%) content of formaldehyde in the preparation.

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TO THE READER

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Our address is:

Mir Publishers

2 Pervy Rizhsky Pereulok

I-110, GSP, Moscow, 129820

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